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Regular vs. As-needed inhaled salbutamol in chronic severe asthma

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Abstract *Study objectives:* Compare as-needed vs. regular use of an intermediate inhaled dose of salbutamol in chronic severe asthma.
Design: This was a 6-week randomized double blind, placebo controlled and crossover study.
Patients and interventions: Ten subjects aged 54.9± 3.35 (mean±SEM) yr under inhaled corticosteroid treatment with persistent severe asthma (FEV_1= 1.87± 0.27 L; 76.9± 6.7%) received salbutamol (100 µg) through an autohaler device, or the corresponding placebo, 2 puffs three times/day; and salbutamol aerosol for symptoms relief. Pulmonary function and sodium metabisulfite airway hyperresponsiveness were measured at baseline and after each study phase. Dairy cards and PEF measurements were revisited.
Results: Mean evening PEF during regularly scheduled salbutamol was lower in comparison with as-needed treatment period (285±33 vs. 295±34 l/min; P= 0.0431). Morning PEF showed a trend in the same direction. There were no differences in: symptom scores, rescue use of salbutamol, FEV_1, $LogPc_{20}$ and doubling doses. Four asthmatic subjects had worse control of asthma during regularly scheduled salbutamol and 4 during as-needed period, as defined by the occurrence of asthma attack. The four subjects that showed worse control with as-needed salbutamol had a significantly lower FEV_1 (1.12 L; P= 0.022. FEV_1% predicted= 52%; P= 0.02), and a lower evening PEF (205 l/min; P= 0.033) after the run-in and as-needed periods in comparison with the other 4 subjects.
Conclusion: Intermediate inhaled salbutamol dose on a regular basis could have some temporary benefit in brittle asthma, but this might not be the case for less severe asthmatic subjects.

Resumen Salbutamol inhalado a dosis fijas versus a demanda en el asma persistente grave. La controversia sobre el uso de los broncodilatadores agonistas de receptores b_2 a dosis fijas versus a demanda no ha sido resuelta para los sujetos con asma grave. Con un estudio de 6 semanas, doble ciego, cruzado, aleatorio y controlado con placebo se comparó el uso a demanda con las dosis fijas de salbutamol en aerosol, 2 aplicaciones de 100 mg tres veces al día o el correspondiente placebo. Intervinieron 10 pacientes asmáticos graves con edad de 54,9 ± 3,35 años (promedio±Error Standard). Todos requerían budesonide en aerosol (dosis diaria = 1.200 ± 103,28 mg). Cada sujeto concurrió 4 veces para revisarle el registro diario de síntomas, los valores de flujo pico espiratorio (PEF) y luego de una espirometría medir la hiperreactividad bronquial con metabisulfito de sodio nebulizado. El PEF vespertino fue la única variable significativamente menor durante la fase con salbutamol fijo que en la fase a demanda (285±33 vs. 295±34 l/min; P= 0.0431). Cuatro sujetos presentaron un peor control en la fase a dosis reglada en tanto otros 4 durante la fase a demanda. Los 4 asmáticos con deterioro del asma durante la fase a demanda tenían: FEV_1 (1.12 ± 0.25 L vs. 2.14 ± 0.22 L; P = 0.022.), FEV_1 % teórico (51.8 ± 10.5 vs. 90.5 ± 6.6; P = 0.02) y PEF vespertino (205 ± 21 L/min vs. 356 ± 51 L/min; P = 0.033) significativamente inferiores durante la fase de ingreso y a demanda que los 4 sujetos que mejoraron durante la fase a demanda. En conclusión, una dosis intermedia de salbutamol en aerosol a dosis fijas podría ofrecer un beneficio temporario en sujetos con asma difícil; pero perjudicaría el control de la enfermedad en el asma menos grave.

Introduction

The debate about the safety and efficacy of regularly scheduled use of b-agonists as a class continues. [1-8] In patients with mild asthma, inhaled salbutamol might be prescribed on an as-needed basis, as was stated by Drazen and colleagues. [1] These authors were unable to demonstrate any additional benefit of regularly scheduled treatment with inhaled salbutamol. Similar conclusion was achieved in mild-to-moderate asthma. [5] However, within severe asthmatic subjects the controversy is still unresolved. Sears and colleagues [2] strongly recommend that inhaled β_2 agonists should be used only on demand and that reduction in dosage may be beneficial in patients with troublesome asthma. The purpose of the current study was to compare regular use of an intermediate inhaled dose of salbutamol vs. as-needed use in chronic severe asthma.

Methods

Inclusion criteria

The inclusion criteria required eligible patients to have diagnosis of persistent severe asthma as defined by the WHO/NHLBI report .[9] To be non- or ex-smoker of less than 10 pack-yr, to be neither pregnant nor breast-feeding and to be capable of measuring peak expiratory flow rate (PEF). To fulfill the following markers of asthma severity, 1) to have been referred to the specialist because of hospitalizations or frequent Emergency Department (ED) visits due to asthma attacks. 2) To be incapable of diminishing the dose of inhaled budesonide below 800 µg/day without a relapse in the last 12 months. 3) To require short courses of oral steroids at least 6 times during the last 12 months. The dose of inhaled budesonide, which was established on clinical grounds before entry into the trial, was maintained throughout the study.

Study design

This was a 6-wk, double-blind randomized, crossover, placebo controlled study in which subjects inhaled 100 µg of salbutamol aerosol through an autohaler device (Salbulin®), generously supplied by 3M Pharmaceutical Argentina, or the corresponding placebo, 2 puffs three times/day. Subjects used salbutamol aerosol (Glaxo Wellcome, Argentina) for symptoms relief throughout the study. The placebo autohaler devices were indistinguishable from the active devices in order to guarantee the double-blindness of the study. The sequence was decided through a random table. During the 2 weeks run-in period, the patients' compliance and capacity to take part in the study were assessed. Daily diaries were maintained by patients throughout the study period to record: 1) Peak expiratory flow rate (PEFR) using a mini peak flow meter (Vitalograph Ltd, Ireland) every morning on awakening and every evening just before the last scheduled aerosol doses; 2) number of puffs of rescue salbutamol inhaler and 3) severity of symptoms on a scale of 0 (asymptomatic) to 5 (worse). Each one of the 3 phases lasted 2 weeks (allowable range 13 to 16 d). The first six days of each phase was considered as a washout period to minimize a carryover effect, thus the last 8 days of each period were used for analysis. In case of asthma exacerbations, patients were allowed to take either supplementary β_2 agonists and systemic corticosteroids while the trial medication was continued. An asthma exacerbation was defined as requiring bronchodilator more than four times per day for 2 consecutive days with a deterioration in symptoms that determined an E.D. visit or a short rescue course (3-6 days) of oral corticosteroids. This event was considered to indicate that asthma control was worse during the treatment period in which the crisis occurred. Within-subject comparisons (paired t test) were made for morning and evening PEF, and symptom scores when there was no systemic corticosteroids requirement. If the significant differences were not in the same direction, better asthma control was defined by applying the following criteria from greatest to least importance: morning PEF, evening PEF, symptom scores, additional bronchodilator use only if it was lower during the period of as-needed treatment.

Assessment of airway responsiveness

All 4 visits were carried out at in the morning. On each visit, after 10 minutes rest, spirometry (Vitalograph compact spirometer [daily calibrated], Buckingham, UK) was performed in triplicate and the best FEV_1 value was taken as baseline FEV_1 if there is less than 5% difference between the two highest values. All the treatments

were withheld for 12 hrs and short-acting bronchodilators 8 hrs before each visit.

The protocol used to perform the sodium metabisulfite (MBS) bronchial provocation test was previously published. [10] Fresh solutions of MBS were made up to produce a range of concentrations in 0.9% saline of 0.3-80 mg/ml. Each solution was administered by continuous nebulization through a face mask with nose clipped at tidal breathing from a De Vilbiss 646 jet nebulizer (DeVilbiss Health Care Inc., Somerset PA. USA) with Venturi opened, driven by 12 l/min of oxygen at a pressure of 20 psi, during one minute. According to published measurements [11] at these conditions, the nebulizer delivered an aerosol with aerodynamic mass median diameter of 3.7 (0.2) µm at an output of 0.27 ml/min. Normal saline was nebulized first, and the study continues if the FEV_1 did not fall more than 10%. Then, FEV_1 was measured two minutes after each inhalation of doubling concentrations of MBS starting at 0.3 mg/ml until a greater than 20% fall in FEV_1 from post saline-baseline value was achieved. If the baseline FEV_1 was lower than 1.0 liters or, less than 30% of predicted, [12] a PC_{20} of 0.3 mg/ml was arbitrarily assigned. All the subjects gave informed consent. The protocol was approved by hospital ethic committee.

Analysis of Data

Each patient's individual mean values for various endpoints were compared between treatment periods by paired t-tests. To assess if there were any differences in the 4 days' FEV_1 values, a two way analysis of variance was used. Results are expressed as mean (standard error of the mean). A log dose-response curve was constructed and the provocative concentration causing a 20% fall in FEV_1 ($logPC_{20}$) was calculated by linear interpolation and expressed in logarithmic (base 10) terms. The $logPC_{20}$ values for MBS after regular salbutamol- and placebo-periods were compared using Student's paired t test and were expressed as geometric mean, that were calculated as the antilogarithm of the mean log PC_{20}. The repeatability of the MBS challenge procedure was previously published. [10] The effect of the treatment periods on MBS provocation was calculated by comparing the $logPC_{20}$ in each subject and expressed in terms of mean (SEM) doubling doses (DD), using the formula= ($logPC_{20}$ regular salbutamol- $logPC_{20}$ run-in period)/log 2 and ($logPC_{20}$ as-needed salbutamol- $logPC_{20}$ run-in period)/log 2. The following end points were compared with repeated meaures analysis of variance: 1) FEV_1 at baseline, after run-in and after each treatment period. 2) morning PEF. 3) evening PEF, 4) diurnal variation in PEF = ({evening PEF - morning PEF} / mean PEF) x 100, 5) minimum morning PEF according to Reddel et al[13], 6) additional doses of salbutamol aerosol, 7) symptom scores, and 8) MBS doubling doses. All of these items mean values obtained after run-in and after each treatment period were compared. A p value of < 0.05 was accepted as the minimum level of statistical significance. All tests were two tailed.

Results

A total of 4 patients potentially eligible that participated in a previous descriptive study,[14] were discontinued during initial screening; one because of concomitant congestive heart failure, another because of moving too far away and two denied to participate. Table 1 shows baseline characteristics. Four asthmatic subjects had worse control during regularly scheduled salbutamol (3 subjects had exacerbations and 1 significantly lower morning PEF). During as-needed treatment period, 3 subjects had worse asthma control as defined by the occurrence of asthma attack and one subject because of lower PEF values and symptom scores. In the remaining 2 patients neither objectives variables nor clinical asthma control showed differences between treatment regimens. Mean evening PEF during regularly scheduled salbutamol period was lower in comparison with as-needed treatment period ($p = 0.043$; table 2). This variable was the only endpoint that differed significantly between treatments. There was no significant sequence effect of sequence/treatment interaction.

The results of the 4 subjects that showed better control of asthma at placebo period was compared (unpaired t test) with the 4 subjects with better control at scheduled salbutamol period. At run-in and placebo periods, subjects that showed better control with scheduled salbutamol had a significantly lower basal FEV_1 (1.12 ± 0.25 L vs. 2.14 ± 0.22 L; $P = 0.022$), lower FEV_1 % predicted (51.8 ± 10.5 vs. 90.5 ± 6.6; $P = 0.02$) and a lower evening PEF (205 ± 21 L/min vs. 356 ± 51 L/min;

Table 1. Baseline characteristics

Subject No.	Age yr/sex	Yrs of asthma	FEV_1 (L)	PC_{20} % Pred.	Budes. mg/ml.	Better mg	period.
1	71/m	30	1.88	82.6	12.69	1200	S
2	46/m	28	3.45	100.3	5.18	1200	Neither
3	45/f	25	1.87	76.7	80	800	PRN
4	45/f	28	2.5	110.5	1.1	1200	PRN
5	47/m	39	2.95	88.5	0.67	800	PRN
6	67/f	47	1.22	65.8	0.89	1200	S
7	62/f	60	1.06	51.8	0.3	800	Neither
8	67/f	18	1.48	90.1	1.18	1600	PRN
9	47/f	15	1.37	58.2	1.2	1600	S
10	52/f	32	0.94	45.0	0.3	1600	S
Mean	54.9	32.2	1.872	76.95	1.84*	1200	
SEM	3.35	4.25	0.27	6.78	4.50	103.28	

**Geometric mean of Sodium metabisulfite concentration that induced a 20% fall in FEV_1 (PC_{20}).*
Budes: inhaled budesonide dose. Better period: phase in which the subject showed a better asthma control. S= regularly scheduled salbutamol. PRN= As-needed period.

P = 0.033) than the group with better control at placebo period. Four subjects required E.D. visits: subjects #3 and #9 during run-in period, subject #5 on scheduled regimen and subject #10 on as-needed treatment period.

Discussion

This double-blind, crossover study could not definitely demonstrate that regular use of inhaled intermediate dose of salbutamol gave a worse control in these patients with severe asthma in terms of number of exacerbations, symptom scores, additional b_2-agonists use and MBS doubling doses. However, evening PEF decreased significantly during regular salbutamol use and morning PEF showed a trend in the same direction. Evening PEF was the unique endpoint that differed between treatment periods (295 ± 34 l/min; vs. 285 ± 33 l/min; p=0.043); but this small difference, though significant, might not be indicating a deleterious clinical effect. The paradoxical lower mean evening PEF during regularly scheduled salbutamol has been described previously and also without a deleterious clinical impact. [15]

Despite the cumulative evidences that support the use of long acting β_2 agonists in association with inhaled steroids, [16] short acting β agonists still deserve to define its role in chronic severe asthma. In day to day practice, despite short acting β agonists are recommended as reliever medication,[9] subjects with difficult to control asthma required increasing doses that resembled a regularly scheduled regimen.

Importantly, poor perception of breathlessness was associated with: severity of asthma in outpatients with different grading of asthma, [17] particularly those with recurrent exacerbations; [18] with elderly asthmatic patients,[19] with long-standing airflow limitation[20] and with asthmatics who experienced near fatal asthma.[21] Regularly scheduled use of salbutamol might be defended in these settings where the poor perception of asthma symptoms could determine an underuse of bronchodilators. Wanner[7] suggested that regular therapy with b_2 agonists at recommended dosages offered around-the-clock protection against bronchoconstriction and therefore, there was no reason to rely on patient symptoms to guide therapy with a safe, prophylactic drug.[7] By contrast, overreliance on b_2 agonists and further unsupervised administration has been associated with poor outcome in noncompliant subjects.[3,22,23] There was a paucity of trials that focused this issue in such a severe asthmatic group as in the current study. The asthma severity in this group was reflected by as follows: 4 ED visits and 11 short courses of systemic corticosteroids within the 6 weeks study period (table 2).

Table 2. Mean values after each study phase

Run-in	as needed	scheduled	
FEV_1 L	1.68(.23)	1.83(.23)	1.64(.23)
% pred	69.97(7.6)	76.77(7.1)	70.52(8.4)
$LogPC_{20}$MBS mg/ml	0.26(0.26)	0.53(0.20)	0.50(0.19)
Geometric mean	1.78	3.36	3.13
Doubling doses		0.90(0.68)	0.81(0.56)
PEF am L/min	288(39)	295(39)	282(31)
PEF pm L/min	290(39)	295(34)	285(33)*
Diurnal variation in PEF	-0.03(2.2)	1.36(2.6)	0.66(2.8)
Additional $ß_2$ agonists	1.6(.5)	1.2(.7)	0.9(.3)
Symptom scores	2.6 (.6)	2.1(.5)	2.4(.5)
No. Exacerbations	4	3	4
E.D. visits	2	1	1

*Values are means (SEM). *Mean Evening PEF (pm) after scheduled treatment period was significantly lower than after as needed period (P = 0.043). E.D.:number of emergency department visits requiring systemic corticosteroids.*

The controversy of regularly scheduled vs. as-needed β_2 agonists in these severe asthmatics could be observed through the following subgroup post hoc analysis. As defined by protocol, the treatment period in which an exacerbation occurred was directly considered as worse asthma control. When the group that had shown better control of asthma during regular inhaled salbutamol was compared with subjects that had a better control of asthma during on demand (placebo) basis, some surprising data were obtained. Subjects that showed better control with scheduled salbutamol had a significantly lower FEV_1 and a lower evening PEF in comparison with the other group at run-in and placebo periods. Hence, it seemed that these four subjects were experiencing a more clinically unstable and troublesome or difficult to control asthma than the rest of the intervening subjects. Under these circumstances inhaled salbutamol on a regular and intermediate dose could have some temporary benefit in view that these patients suffered more exacerbations during on as-needed basis. Despite the small sample size that was the main weakness of the post hoc analysis, lung function values at run-in and placebo (as-needed) periods were significantly lower between subjects with difficult to control asthma than in the less severe subgroup. This difference could explain why the difficult to control asthma group might have beneficiated with scheduled salbutamol. This group of subjects shared most of the features associated with poor perception of asthma symptoms described above.[17-20] More recently, Magadle and colleagues prospectively confirmed that asthmatic subjects with low perception of dyspnea are at higher risk of hospitalization, near-fatal and fatal asthma. [24] The low mean of daily rescue puffs of salbutamol and symptom scores registered during run-in and on demand periods might be related with the poor perception of breathlessness in brittle asthma.[18] Furthermore, a study suggested that two distinct pathologic, physiologic, and clinical subtypes of severe asthma exist. [25] Patients with difficult to control asthma may develop exacerbations that cannot be prevented by even high doses of inhaled corticosteroids. An eosinophil independent mechanism may explain why some patients are difficult to control. [25-26] Furthermore, budesonide enhances the perception of airway narrowing, but the effect is unrelated to budesonide dose, or to changes in circulating eosinophil markers. [27] More studies are needed to disclose a relationship between lack of eosinophils during exacerbations and better outcome under regularly scheduled salbutamol.

This study had some limitations, further than the small sample size. First, some patients achieved a near normal FEV_1 % predicted but under high doses of inhaled budesonide, so they should be considered as severe. Second: requiring inhalations 4 times a day while would have been pharmacologically optimal in treatment with salbutamol, would have seriously affected compliance, and some adverse effects could have revealed the drug tested. A 43 % reduction in mean weekly salbutamol dosage resulted in the same control of symptoms in moderately severe asthma.[28] A cohort analysis of mortality from asthma found a change -point dose-response curves indicating that the risk of asthma death began to escalate drastically at a consumption about 2.1 (95% CI: 1.7 to 2.7) canisters (of 20,000 µg each) per month of inhaled β-agonist. That means a daily dose around 11 puffs as the recommended lower limit (340 puffs represent the lower limit of the 95% C.I. and divided by 30 days: 11 puffs). [29] Thus, an intermediate regular dose (2 puffs 100 µg each, three times a day) was selected because it was undoubtedly below the lower limit of the 95% C.I. risk dosage. [29] According to the protocol, subjects were in-

structed to seek medical attention if they required more than 4 puffs of salbutamol for 2 consecutive days without improvement. Then, the total dose of inhaled β-agonist rarely could have exceeded the above mentioned recommended lower limit of 11 puffs per day, even during the regularly scheduled salbutamol period (6 puffs/day). This apparent too meticulous restriction for using salbutamol was oriented to preclude overreliance in salbutamol and a delay in seeking help. It should be mentioned that the risk was not the salbutamol overuse in it itself .

Assessment of airway hyperresponsiveness (AHR) with indirect bronchoconstrictor stimuli such as MBS, may be a truer reflection of clinical asthma. [30] However, the relationship between AHR, airway inflammation and obstruction is still weakly demonstrated. [31] It could not be found an increased sensitivity to MBS following regular salbutamol in these subjects; in contrast to another study that showed an increased sensitivity to bradykinin after 7 days of regular salbutamol. [32]

Finally, the clinical implications of this study are that difficult to control asthma could obtain a temporary benefit with a regularly scheduled intermediate dose of inhaled salbutamol, but this might not be the case for subjects with less severe asthma.

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