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Assessing physiological benefit from domiciliary nebulized bronchodilators in severe airflow limitation

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ABSTRACT: In steroid resistant chronic obstructive pulmonary disease (COPD) we assessed the effect of *q.i.d.* domiciliary nebulized fenoterol (F) 1.25 mg and ipratropium (I) 0.5 mg for three weeks in a placebo-controlled, randomized, double-blind, crossover study.

The twenty patients studied (mean forced expiratory volume in one second (FEV_1) 0.8 *l*) all showed <20% increase in FEV_1 to 200 μg inhaled salbutamol (S) and <20% increase in peak expiratory flow rate (PEFR) after 2 weeks prednisolone therapy. Respiratory function tests, 5 min walking distance (5 MWD), visual analogue scales (VAS) for breathlessness, oxygen cost diagrams and reversibilities were performed weekly for three weeks with patients on their usual therapy, after three weeks domiciliary F+I, after three weeks saline and, finally, after a further three weeks on usual therapy again. Primary end-points, selected prior to unblinding, were mean home twice daily PEFR, trapped gas volume, FEV_1 and 5 MWD.

Home PEFR rose from 164 $l \cdot min^{-1}$ on saline to 196 $l \cdot min^{-1}$ on F+I (p=0.0001). Secondary end-point analysis revealed a fall in home inhaler usage and a rise in VAS.

Using the criterion of +15% and >20 $l \cdot min^{-1}$ increase in home PEFR, 11 out of 20 patients had a "positive" trial. We suggest that such patients, but not others, benefit from long-term, nebulized β_2-agonist and ipratropium. Trials using home PEFR recordings should be used to identify them.

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It is difficult to manage a severely disabled patient with breathlessness due to chronic obstructive pulmonary disease (COPD). Such patients frequently request domiciliary nebulizer treatment for symptom relief. They are usually those who have initially been managed by smoking cessation advice and optimization of the dose and technique of bronchodilator therapy by regular metered dose aerosol (MDI). It is then common practice to assess steroid reversibility and subsequently to use either inhaled or oral steroid maintenance therapy in those who appear to bronchodilate [1, 2]. Unfortunately, many patients are unresponsive to all of these measures, and to oral theophyllines, and are labelled "irreversible". A decision then has to be made whether or not to recommend domiciliary nebulizer treatment.

The evidence that high dose beta-agonist treatment by nebulizer produces better bronchodilatation than standard MDI doses in the laboratory setting is very convincing [3–6]. However, the evidence that patients may subsequently show persistent bronchodilatation in the longer term is not so convincing. Nevertheless, such treatment is widely prescribed [7, 8].

Although it would be expected that high dose bronchodilator therapy by nebulizer should produce long-term physiological benefit in such patients, definite evidence that this happens is lacking. Furthermore, it is not known which method or methods of measuring physiological benefit are appropriate for longer term comparisons.

Nearly all of the published studies of domiciliary nebulizer treatment in chronic asthmatics and mixed groups of COPD patients have used β_2-agonists only [9–13]. However, there is now good evidence from laboratory work that a high proportion of the more elderly patients with a predominantly smoking-related COPD may bronchodilate further if ipratropium is added [14–16]. The combination of a β_2-agonist and an anticholinergic may bronchodilate these patients better than maximum doses of either drug, given singly [17–19].

Because of these uncertainties, we have studied the physiological responses to a combination of a nebulized β_2-agonist and an anticholinergic in a group of patients with stable severe COPD. We made multiple and detailed physiological measurements during a prolonged run-in period and then compared these measurements during randomly allocated periods of nebulizer treatment using either saline or a combination of a β_2-agonist and

an anticholinergic. We then examined the data to see if bronchodilatation or any other physiological benefit could be detected and which tests appeared to demonstrate this.

Method

Patients were recruited serially from an out-patient chest service. Preliminary inclusion criteria were breathlessness due to COPD for more than 2 yrs, an FEV_1 of <50% predicted, and an FEV_1/FVC ratio of <60%. Patients who were willing to be further assessed then had a formal reversibility test with 200 μg salbutamol (S) or 360 μg fenoterol (F) by inhaler, after more than 6 h on no β_2-stimulant treatment. They also had an out-patient trial of oral corticosteroids, taking 20 mg daily prednisolone for 2 weeks, and keeping a twice daily peak flow chart at home. Patients with a <20% increase in FEV_1 after the bronchodilator aerosols, and a <20% increase in mean peak flow rate at the end of the steroid treatment, were then considered for the study. No patients had any other systemic disease, or symptomatic cor pulmonale.

All patients studied gave informed, written consent, and the protocol was approved by the Leeds Eastern Health Authority, Clinical Research Ethics Committee.

Study outline

Patients completed a 3 week run-in period, followed by two randomly allocated 3 week periods of nebulizer treatment and then a further run-out period of 3 weeks. During the run-in and run-out periods patients took their normal bronchodilator inhaler treatment at home, and during the nebulizer periods noted the number of "rescue" puffs of inhaler needed per day.

After prior instruction in the laboratory, patients recorded, throughout the study, the best of three peak expiratory flow rate (PEFR) readings (Wright mini peak flow meter, Airmed UK Ltd), before treatment on waking and at 6 pm every day. Full laboratory assessments were performed after weeks 1, 2, 3 (run-in), after weeks 6 and 9, and after week 12 (run-out). After week 3, patients were given a compressor (Medix Traveller, Airmed Ltd), an Inspiron minineb nebulizer and a face mask or T-piece, and instructed to treat themselves at home for 10 min, four times a day, using unit dose vials (UDVs), containing either 1.25 mg F with 0.5 mg I (Isotonic and preservative free) for 3 weeks, or identical UDVs containing saline as a placebo for 3 weeks. UDVs were given double-blind and their order was randomized. The compressor generates an airflow of 6 $l \cdot min^{-1}$ and the nebulizer produces an aerosol with an aerodynamic mass median diameter (MMD) of 6 μm [20].

Laboratory assessments

Before each laboratory visit patients omitted their previous dose of bronchodilator treatment. The following physiological measurements were made at the same time of day for each individual patient: peak expiratory flow rate (Wright peak flow meter, Airmed UK Ltd), spirometry (Vitalograph dry wedge spirometer), lung volumes by body plethysmography (Gould Autobox 2800) and by helium dilution using a modified water-filled Collins spirometer. Transfer factor was measured using the carbon monoxide single-breath method and the Collins spirometer. Specific airways conductance and maximum inspiratory and expiratory flow volume loops were obtained using the body plethysmograph. All of these tests were repeated at each attendance one hour after 5 mg S and 0.5 mg I by nebulizer. Patients also performed three 5 min walking tests on each day, starting from a fixed point and separated by at least 30 min rest [21]. Psychological factors were assessed at each visit by the hospital anxiety depression (HAD) score [22], breathlessness on exertion was assessed by a visual analogue scale (VAS), administered before and after a 5 min walk, and overall subjective exercise capacity by a Borg oxygen cost diagram [23] and a 20 point exercise difficulty score.

At entry, blood carboxyhaemoglobin (CoHb) was measured by differential spectrophotometry, a total serum immunoglobulin E (IgE) was measured by Phadebas-IgE radio-immunoassay (RIA), and Phadebas radio-allergosorbent test (RAST) screen (house dust, house dust mite, cat, grass, *Aspergillus fumigatus*) and an eosinophil count were performed. All patients were using metered dose bronchodilator aerosols. Treatment was not standardized and patients were instructed to continue their usual medication throughout the run-in and run-out periods. No patients were taking oral steroids or oral theophyllines.

Analysis

We considered four measurements as those most likely to show some physiological improvement, and nominated these as primary end-points of the study prior to unblinding. They were home peak expiratory flow rate (PEFR), baseline laboratory FEV_1, the difference between Box and Helium lung volumes (trapped gas volume (TGV)) [24], 5 minute walking distance (5 MWD) [25]. The other parameters outlined above, together with documented inhaler usage, were considered as secondary end-points.

Statistical analysis was made using analysis of variance for comparisons with "usual inhaler" and Student's paired t-tests for comparisons between saline and F+I, having tested for normality using the Shapiro-Wilk statistic with Royston's approximate normalizing transformation. Where there was evidence of deviations from normality, a Wilcoxon signed rank matched pairs test was used.

Results

Twenty four patients entered the study of whom four were withdrawn because of intercurrent infections during the run-in period. The baseline data on the remaining 20 patients are shown in table 1. The physiological measurements are taken from week 3, since analysis showed that any learning effect in performing tests had plateaued by then, and these values were taken as a baseline for subsequent comparison.

Table 1. – Baseline data for all patients (n=20)

Parameter	Mean	±SD	Range
M/F	8:12		
Age yrs	66		49–75
Ht cm	162.1		147–178
Wt kg	61.4		47–87
FEV_1 *l* B	0.81		0.32–1.16
A	0.93		0.57–1.64
FVC *l* B	1.10	±0.30	
A	2.32	±0.20	
FEV_1/FVC B	40	±4.7	
Home PEFR $l \cdot min^{-1}$	167		75–350
Lab PEFR $l \cdot min^{-1}$	145	±21.4	
TLC Box *l*	6.47	±0.5	
TLC He *l*	4.85	±0.64	
Trapped gas *l*	1.62	±0.68	
FRC *l*	4.66	±0.50	
RV *l*	3.82	±0.52	
sGaw $l \cdot s^{-1} \cdot kPa^{-1}$ B	0.5	±0.15	
A	0.58	±0.15	
TF $ml \cdot min^{-1} \cdot kPa^{-1}$	3.02	±0.87	
FEF 50%	0.37	±0.08	
5 MWD m	272		140–429
Breathlessness B	2.49	±1.06	0–8.7
A	7.39	±1.03	2.3–9.3
Difficulty walk	14.5	±1.33	11–19
O_2 cost	4.59	±0.74	2.9–6.0
HAD A	7.25	±1.63	1–16
D	6.4	±1.13	2–13
CoHb %	1.37	±0.78	1.0–4.2
Eos	2.61		0.3–5.9
IgE	133.5		20–680
Rescue puffs·day^{-1}	8.4	-	1–14

M: male; F: female; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; PEFR: peak expiratory flow rate; Lab: laboratory; TLC: total lung capacity; FRC: functional residual capacity; RV: residual volume; sGaw: specific airways conductance; TF: transfer factor; FEF 50%: forced expiratory flow at 50% vital capacity; 5 MWD: five minute walking distance; HAD: hospital anxiety index, A = anxiety D = depression; CoHb: carboxyhaemoglobin; Eos: eosinophils; IgE: immunoglobulin E; B and A: before and after exercise.

The patients had severe airflow obstruction, with a mean FEV_1 of 0.81 *l* (33% predicted) and a mean FEV_1/FVC ratio of 40%. As a group they all had marked hyperinflation and a mean trapped gas volume of 1.62 *l* and a functional residual capacity of 4.66 *l*.

Inspection of the run-in PEFR recordings showed no appreciable diurnal rhythm (>20 $l \cdot min^{-1}$) in any patient. Subsequent analysis therefore used the mean of all the 14 measurements of the whole of each week in the run-in period and in the last week of each of the nebulizer and run-out periods. The mean pretreatment PEFR was 167 $l \cdot min^{-1}$. The patients had a mean 5 MWD of only 272 m and increased their mean breathlessness score from 2.49 to 7.39 after exercise. The HAD scores showed a considerable amount of pretreatment anxiety, with six patients scoring 10 or more at week 1, compared with three after week 3. For depression, five patients scored 10 or more at week 1, compared with five after week 3.

There was no significant difference in the mean physiological variables between week 3 and week 12 post-study.

All patients had four reversibility studies whilst on usual treatment. The variability and reproducibility of such tests is described elsewhere [26]. For the tests in week 3, before randomization to nebulizer treatment, the mean increase in FEV_1 was 0.12 *l* (range -0.05 to +0.58 *l*; SD±0.15). However, if the criteria for genuine reversibility (*i.e.* with a 95% confidence interval (CI) to exclude random variation) suggested by NISAR *et al.* [3] and TWEEDALE *et al.* [27] are applied, only 4 of the 20 (20%) subjects showed a bronchodilatation of >15% and at least 0.2 *l*. We concluded that these patients, as well as being relatively resistant to steroid treatment, showed, as a group, little bronchodilatation with conventional laboratory tests using nebulized drugs.

CoHb was measured in all patients three times during the run-in period. Only two measurements in one patient were ≥4% and the average value at 3 weeks was 1.37%, indicating that the patients were predominantly nonsmokers at the time of study. Two patients had eosinophil counts of >500·μl^{-1}, and six had an IgE of >125 $\mu \cdot ml^{-1}$, but only two patients had any RAST class >1+ on any test. Self-reported regular bronchodilator inhaler usage pre-test ranged between 1–14 puffs·day^{-1} (mean 8.4 puffs·day^{-1}).

Primary end-points

If multiple measurements are made on patients in a study like this, then by chance an average measurement may appear to change by a conventionally significant amount *e.g.* $p<0.05$. For this reason, prior to unblinding, we nominated four measurements (home PEFR, FEV_1, TGV, 5 MWD) as primary end-points of particular interest, and the level at which significance was accepted was reduced according to their correlations. With the evidence from this study that these end-points were correlated at about r=0.1, the level at which significance is reached for each end-point is p=0.013 [28]. This maintains an overall significance level of $p<0.05$ when all four primary end-points are considered.

Secondary end-points

The secondary end-points were analysed similarly and also using multiple regression and stepwise methods to identify which variables were most affected by

treatment. No statistical significance is associated with these parameters.

All patients completed the two nebulizer periods and the follow-up period of 3 weeks. The comparison of the primary end-point changes between saline and F+I is shown in table 2. Home peak flow was clearly increased by F+I from 164 to 196 $l \cdot min^{-1}$ (p=0.0001), whilst no effect was demonstrated on TGV or FEV_1. Walking distance exhibited some period effect with better walks when saline was given first (+21 m, p=0.0123), whilst the effect was smaller when the drugs were given the other way around (+4 m, p>0.05). Overall the difference did not reach the required level of significance, the mean difference between placebo and active treatment being 12 m (5%). No such order effect was seen with the other primary end-points.

Table 2. – The change in all primary and selected secondary end-points, comparing nebulized fenoterol and ipratropium with nebulized saline

Variable	Mean change	SE	p
Primary end-points			
Home PEFR $l \cdot min^{-1}$	32.35	4.96	0.0001
Walking distance m	12.26	5.06	0.0254
FEV_1 l	0.06	0.06	>0.05
TGV l	-0.15	0.23	>0.05
Selected secondary end-points			
Lab PEFR $l \cdot min^{-1}$	17.85	6.75	0.0159
FIF 50% l	0.62	0.17	0.0046
PIF $l \cdot s^{-1}$	0.66	0.21	0.0285
FEF 50%/FIF 50%	-0.06	0.016	0.0052
O_2 cost VAS	0.76	0.22	0.01
Home inhaler puffs	-3.9	0.73	0.0001

TGV: trapped gas volume; FIF 50%: forced inspiratory flow at 50% vital capacity; PIF: peak inspiratory flow; VAS: visual analogue score. For further definitions see legend to table 1.

The average home PEFR increase was 32.3±4.96 (SE) $l \cdot min^{-1}$. This is a mean increase of 19% from a baseline of 167 $l \cdot min^{-1}$. Fifteen patients had increases of >20 $l \cdot min^{-1}$, and 12 out of 20 had a percentage increase of >15% and 10 >20%. Eleven patients had a home PEFR increase of >20 $l \cdot min^{-1}$ which was >15% baseline: *i.e.* only 1 out of 12 patients had an increase of 15% which was <20 $l \cdot min^{-1}$ (actual value 18 $l \cdot min^{-1}$).

Analysis of variance revealed no difference between visits 3 and 12 (both on usual treatment). When nebulized F+I was compared with the usual treatment (mean of visits 3 and 12) there was no difference in trapped gas volume, FEV_1 or walking distance. However, home peak flow was substantially increased by the nebulized drugs (36 $l \cdot min^{-1}$, p<0.0001). The primary end-point analysis, therefore, showed a significant improvement in home PEFR between active nebulizer treatment and both saline nebulizer treatment and usual inhaler treatment, whereas other measures showed no significant changes.

Secondary end-points

The results are shown in table 2. Overall, the data suggested that compared with placebo, F+I increased laboratory measured peak flow, oxygen cost VAS, forced inspiratory flow at 50% of vital capacity (FIF 50%) and peak inspiratory flow (PIF). Also, the number of puffs of bronchodilator used whilst on F+I and the ratio of forced expiratory flow (FEF) 50% to FIF 50% were decreased as compared to placebo. Changes in other variables were probably due to random variation. Multiple regression on the primary and secondary end-points together, using both forward and backward elimination processes, confirmed that the home peak flow was the only important variable that related to the change in treatment, since although other variables were affected by treatment, they tended to be correlated with home peak flow. The acute bronchodilator challenge in the laboratory as determined by changes in peak flow and spirometry failed to predict which patients responded to the F+I at home as measured by home peak flow (fig. 1).

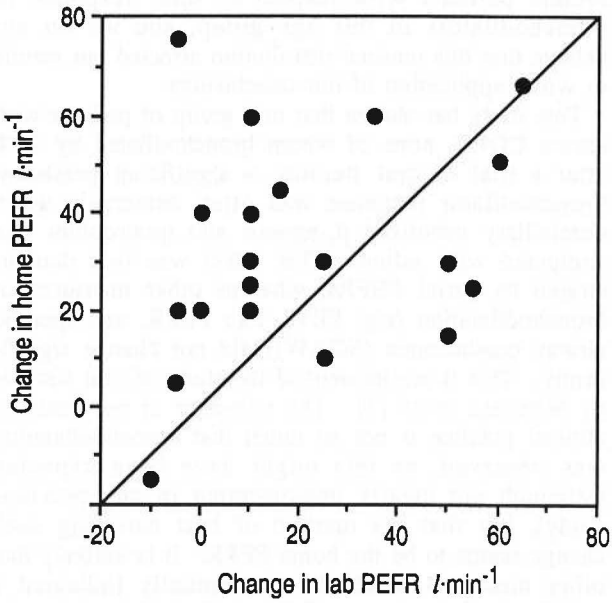

Fig. 1. – A comparison of the change in peak flow rate after hospital bronchodilator challenge with 5 mg salbutamol on week 3, and the change at home after nebulized fenoterol and ipratropium compared with saline. Similar poor correlations were demonstrated for both the FEV_1 and the FVC. FEV_1: forced expiratory volume in one second; FVC: forced vital capacity.

Fifteen patients stated that they felt better whilst on nebulized F and I, one was better on placebo and four did not notice a difference. The relationship between the subjective responses and patients peak flow responses is discussed below.

Side effects

Twelve patients reported side-effects, 10 whilst on F+I and two on both treatments. Side-effects were graded by the patients themselves as mild, moderate or

severe. Tremor was the most frequent side-effect (8 mild and 1 severe on F+I, 1 moderate on placebo). Dry mouth was seen in five patients on F+I (2 mild, 2 moderate, 1 severe) and one patient complained of nausea on F+I. No patient withdrew because of these effects.

Discussion

Patients

The age group and physiology of our patients resembled those in similar studies, but there was, unusually, a female preponderance. Patients were recruited sequentially from an out-patient service and no selection was applied. Only patients willing to have multiple laboratory visits and measurements made were recruited and this may explain why there was not the expected male preponderance. We know of no evidence, however, that there is a difference between male and female patients with respect to their response to bronchodilators in this age group, and we do not believe that this unusual distribution affected our results or wider application of our conclusions.

This study has shown that in a group of patients with severe COPD, none of whom bronchodilated by 20% after a trial of oral steroids, a significant persistent bronchodilator response was often detectable when domiciliary nebulized β_2-agonist and ipratropium was compared with saline. This effect was best demonstrated by serial PEFRs, whereas other measures of bronchodilatation (*e.g.* FEV_1, Lab PEFR, and specific airway conductance (SGAW)) did not change significantly. This is reminiscent of the study of oral steroids by MITCHELL *et al.* [1]. The relevance of our result to clinical practice is not so much that bronchodilatation was observed, as this might have been expected (although not clearly demonstrated in any previous study), but that the method of best detecting such change seems to be the home PEFR. It is unlikely that other measures would have eventually indicated a significant change, even if the study had been greatly expanded in numbers. The home PEFR would appear to be the most sensitive and reliable index of longer term bronchodilatation in these patients.

A change in FEV_1 of 15% with a bronchodilatation of at least 0.2 *l* has been shown to be a reliable index of reversibility in laboratory tests in patients with severe COPD [3]. Our suggestion is, therefore, that for an individual patient, a change in PEFR of 15% and 20 $l \cdot min^{-1}$ is taken as indicating a definite bronchodilator effect after domiciliary nebulizer treatment, and such patients might then be considered, after study, as suitable for longer term treatment. In our study 11 of 20 patients would so qualify. We have subsequently studied a further 100 patients, 28% of whom bronchodilated similarly when treated with a combination of nebulized salbutamol and ipratropium, compared with saline [29].

Psychometric scores

Some studies have suggested that a patient's subjective response to a treatment might be as useful as objective measurements in defining "response" because they are likely to be strongly correlated with objective changes [30]. Clearly there has to be a placebo arm for comparison in any assessment. We found that none of the several measures we used to assess breathlessness were strongly correlated with the PEFR response, except for the VAS before and after exercise. The HAD scores did not differ between the treatment and saline arms, although the anxiety scores of several patients fell during the run-in period.

The correlation between overall treatment preference and PEFR result was more impressive, however. Ten out of 12 patients with a PEFR improvement >15% on the active treatment preferred it. However, 5 of the 8 patients with a <15% improvement also did so, although three of these had changes of 14, 13 and 14%. With a >20% change in PEFR, 7 out of 9 preferred the active drugs, whereas with a <20% improvement, 8 out of 11 did so. If subjective preference was to be accepted as an end-point, then 15 out of 20 of the patients would have reported a "positive" trial. It is clear, therefore, that the correlation between "preference" and objective response is not accurate enough for the former to be used alone in clinical practice.

Other studies

Long-term out-patient studies in this group of patients are difficult to perform and this may be why there are relatively few of them [9–13]. Notable amongst these is the study reported by O'DRISCOLL *et al.* [31] in which 34 patients with COPD, mean FEV_1 0.7 *l*, and mean PEFR 168 $l \cdot min^{-1}$, increased the latter to 186 $l \cdot min^{-1}$ after 1 month on 1 mg terbutaline plus 80 μg ipratropium *q.d.s.* by MDI and spacer, 180 $l \cdot min^{-1}$ using 5 mg salbutamol by nebulizer, 178 $l \cdot min^{-1}$ using ipratropium 0.5 mg by nebulizer, and 196 $l \cdot min^{-1}$ using salbutamol plus ipratropium. These results are similar to our own. The correlation between subjective benefit and objective PEFR responses was similar; 25 out of 33 patients who preferred nebulizer treatment had their highest PEFR during it. Conversely, 8 (24%) preferred nebulizer treatment but had a lower PEFR during it.

Conclusion

Our study has shown that patients with severe COPD who do not bronchodilate readily to steroids or in the short-term to β_2-agonists, may do so if treated with a domiciliary nebulizer for several weeks. The best technique to recognize this seems to be to measure the PEFR at home. Laboratory tests of reversibility cannot predict this response and intermittent laboratory measurements are not correlated strongly with it. Better correlations exist between a PEFR response, a

reduction in rescue inhaler usage, an increase in 5 MWD and subjective benefit.

We recommend that domiciliary nebulizer treatment is considered in patients of this type who show at least a 15% increase in monitored PEFR and who subjectively benefit. Patients who show a marked (*e.g.* >20%) reversibility to β_2-agonists may behave differently and their laboratory tests may perhaps predict reversibility in the longer term.

Further prospective studies to examine these conclusions and the benefit of nebulized treatment over several years are now needed, since nebulizer treatment should be contra-indicated if it is physiologically useless, and should be prescribed only if patients have been shown to benefit from it.

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