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# The role of domiciliary nebulizers in managing patients with severe COPD

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The difficulty of assessing nebulizer responses in chronic obstructive pulmonary disease (COPD) has been demonstrated before. This study aims to re-examine both the role of domiciliary nebulizers in COPD and also bronchodilator (BD) assessment in individuals. In a double-blind, randomized, cross-over trial, 19 stable patients with severe COPD were given the following medication 6-hourly for 2-week periods: (1) nebulized salbutamol 2·5 mg with ipratropium 0·5 mg and placebo inhalers (MDI) with spacer; (2) placebo nebules and inhaled salbutamol 400 $\mu$g with ipratropium 80 $\mu$g via MDI with spacer; (3) inhaled salbutamol 400 $\mu$g with ipratropium 80 $\mu$g via MDI with spacer (but no placebo nebulized drugs).

Both nebulized and MDI drugs produced highly significant improvements in forced expiratory volume in 1 sec ($FEV_1$), forced vital capacity (FVC), specific airways conductance, 6-min walking distance (6MWD) and residual volume. There were no significant differences between BD responses obtained after active nebulized and active MDI BDs. From the diary cards, 2 weeks of active nebulized BDs produced a slightly higher median peak expiratory flow (PEF) than active MDI BDs (236 and 219 $l\,m^{-1}$, respectively, $P=0{\cdot}01$) and slightly less extra inhaler use (0·8 and 1·1 puffs, respectively, $P<0{\cdot}05$) but no significant difference in dyspnoea or quality of life (QOL) scores. There were significant correlations between domiciliary PEF and acute BD-induced changes in FVC and 6MWD, and also between domiciliary dyspnoea scores and acute changes in both total lung capacity and 6MWD.

In conclusion, nebulized medication conferred little clinical advantage over the regular use of inhalers with spacers in this group of patients with severe COPD. However, acute changes in total lung capacity, FVC and 6MWD may be useful predictors of the longer-term effects of nebulized BDs in individual patients.

**Key words:** COPD; nebulizers; bronchodilators.

 

## Introduction

Nebulizers are generally given in order to quickly and conveniently deliver large doses of bronchodilators (BD) to patients with severe airflow obstruction, but their domiciliary use remains controversial. This is partly because of the possible side-effects from high dose treatment, partly the fear that patients may rely on the nebulizers rather than seek medical help when they are acutely ill, and also partly for financial reasons. Nebulizer solutions of BD are very expensive and potentially there is a large population of patients with chronic obstructive pulmonary disease (COPD) who might like or who might require them.

A number of studies have shown that similar BD effects can be achieved in COPD patients with metered dose inhalers (MDI)—with or without spacing devices—as with the more glamorous nebulizers (1–5). Other early studies have suggested that acute laboratory studies can be used to identify optimal treatment for individual patients (6,7). However, large placebo responses to nebulizer treatment have also been demonstrated in such patients (3).

Unfortunately, most methods used to assess the possible benefits of nebulized BDs have limitations. Indeed, several studies reported poor correlations between the effects of BD drugs on spirometric indices performed in the laboratory and the subjective responses to these medications during domiciliary trials (8–10). These authors have suggested that domiciliary trials should be the prime method of nebulizer assessment. This has now constituted one of the recommendations in the BTS Guidelines for the use of nebulizers (11). However, once a patient has a nebulizer at home it is difficult to retrieve it because of the well recognised, potent placebo effect of these devices in patients with severe, but minimally reversible, lung function abnormalities (6,7). Some patients feel better simply after feeling any cool nebulized aerosol on their face (8). Possibly supplying a

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nebulizer with nebulized isotonic saline plus BDs in smaller doses from MDIs may produce the same effect. On the other hand, it is possible that the patients' perception is correct and we have been measuring the wrong parameter. The aims of this present study are to determine whether in patients with severe COPD:

- BDs produce greater effects when given via a nebulizer than when given in conventional doses via MDIs both in the laboratory and in the domiciliary setting;
- there is a significant placebo effect from receiving a nebulized aerosol;
- acute BD responses of lung function, walking distances and quality of life score in the laboratory, can predict longer term effects at home.

# Methods

## SUBJECTS

Twenty patients with severe but stable COPD, whose exercise tolerance was limited by dyspnoea, entered this study. There were 11 male and nine female patients, with an age range of 57–79 years. All patients had a chronic productive cough and were either current smokers of at least 20 pack-years ($n = 8$) or were ex-smokers. They all had a stable forced expiratory volume in 1 sec ($FEV_1$) over the preceding 3 months and this was less than 50% predicted normal. None had cor pulmonale and none had any other disease which limited either their exercise capacity or the dose of BD which they could take. No patient had a chest infection within 1 month of starting the study. All patients gave written, informed consent for the study, which was approved by the Lewisham and North Southwark Committee on Ethical Practice.

## PROTOCOL

This was a double-blind, placebo-controlled, randomized, cross-over trial. For 2-week periods patients took 6-hourly medication which comprised either:

- salbutamol 2·5 mg + ipratropium 0·5 mg nebulized and placebo via MDI (active BDs nebulized);
- saline nebulized and salbutamol 400 $\mu$g + ipratropium 80 $\mu$g via MDI (placebo nebulizer + active BDs by MDI);
- salbutamol 400 $\mu$g and ipratropium 80 $\mu$g via MDI and no nebulizer issued (this was always the final period and was not blinded).

All nebulized solutions were made up to 4 ml and nebulized via an ECOneb 26262 nebulizer–compressor unit (Medix, Lutterworth, U.K.) which delivers airflow at 8 l $min^{-1}$ at 20 psi. This was used with an Intersurgical nebulizer and a facemask, which delivers aerosol particles with a mean mass diameter of 3·46 $\eta$m at 8 l $min^{-1}$ flow rate. The active nebulized salbutamol and ipratropium were given as Combivent. The MDIs were used in conjunction with a volumatic spacing device, using two maximal breaths per puff from the inhaler. The volumatic was wiped with an anti-static cloth before use.

## MEASUREMENTS

During each 2-week study period patients kept diary records of:

- their peak expiratory flow (PEF)—the best of three measurements—measured twice daily 1 h after their morning and evening BDs;
- extra (rescue) inhaled BD usage;
- nocturnal wakings due to dyspnoea;
- dyspnoea (on a scale of 1–5);
- the effect of dyspnoea on their quality of life and daily activities (on a scale of 1–5).

Altogether, patients were seen in the laboratory on four occasions. Firstly, they were seen before the study to practice both the lung function tests and the walks. They were then issued with the medication and seen after each study period, when they performed lung function tests and a 6-min walking test (6MWD) (12–14) 1-h after the same BDs which they had been taking for that 2-week period. On each study day:

- both body plethysmograph and spirometer were calibrated;
- total lung capacity (TLC), residual volume (RV) and specific airways conductance (sGaw) (derived from airways resistance) were measured in a constant volume computerized whole body plethysmograph. Six measurements of each were made to derive mean values (these measurements were not made on the last day);
- the best of three technically satisfactory measurements of $FEV_1$, forced vital capacity (FVC) and slow vital capacity (SVC) were obtained with a dry spirometer;
- patients completed a Hospital Anxiety-Depression Score (HAD) (15), a St George's Respiratory Questionnaire (SGRQ) (16,17) and a short St George's questionnaire (SG30) (18,19);
- 6MWD tests were performed along indoor hospital corridors. The subjects were accompanied by one of the investigators who walked in front, encouraging the patients to walk as fast as they were able and to restart as soon as possible if they stopped. At the end of the walks, exertional dyspnoea was recorded on a Borg score and on a 100 mm visual analogue scale, with 0 as no dyspnoea and 100 mm as the worst imaginable breathlessness.

## ANALYSIS

The primary endpoints for the study were $FEV_1$, SGRQ scores, 6MWD and home PEF values. The secondary endpoints were TLC and RV, sGaw and diary card symptom scores. Wilcoxon rank tests were used to compare measurements before and after BDs and also to compare the BD-induced changes due to active nebulizer with those

on active inhaler treatment. Non-parametric analysis, using Spearman's correlation coefficients, was used to compare the laboratory data obtained from acute BD testing and the data obtained from the domiciliary use of the nebulizers, since these data were not linearly distributed.

## Results

One patient developed a chest infection and withdrew from the study, leaving 19 patients, whose demographic details are shown on Table 1, for evaluation. The mean baseline $FEV_1$% predicted of the group was $34 \pm 8$ % (SD) and the mean 6MWD was 429 m $\pm$ 143 m (SD). Table 2 shows the highly statistically significant improvements in lung function and walking distances induced both by nebulized and by MDI BDs in the group as a whole, with increases in $FEV_1$, FVC, SVC, sGaw and 6MWD, and decreases in RV, VAS and Borg post-exertional dyspnoea scores. There were no statistically significant differences between the changes in lung function and walking distance induced by the different regimes in the group as a whole (Fig. 1).

The post-nebulizer $FEV_1$ and FVC were greater than post-MDI by 200 ml or more and 6MWD by 15 m in only three of the 19 patients. The individual changes in $FEV_1$, FVC and walking distance after nebulized and MDI BDs are compared by Bland–Altman plots in Fig. 2. In general, there was no difference between the two methods of administration in terms of spirometry and walks. After nebulizer, a 200 ml or more rise in $FEV_1$, and a 400 ml rise in FVC was seen in 11 subjects and a 30 m increase in 6MWD was found in 10 patients. By contrast, after MDI BD with placebo nebulizer, $FEV_1$ increased by 200 ml or more in 13 patients, FVC increased by 400 ml or more in 14 patients and 6MWD increased by 30 m or more in eight COPD patients.

There were no significant differences in the quality of life scores from the St George's questionnaires and the HAD scores after the three study periods (Table 3), apart from a trivial improvement in the activities score after nebulized BDs compared with placebo ($P < 0{\cdot}05$). However, comparing nebulizer with MDI only, no significant difference in activities scores were found. By contrast, the mean of the morning and evening PEF readings were significantly better on nebulized BDs compared with MDI medication, whether MDI drugs were given with or without accompanying nebulized placebo. Nevertheless, this difference of 17–18 l min$^{-1}$ was small in clinical terms and in only two patients did the mean PEF for the 2-week period exceed 20 l min$^{-1}$ (22 and 45 l min$^{-1}$). Patients took slightly more rescue inhalers when they had no nebulizer at home.

Finally, we tried to establish which acute laboratory test might predict the domiciliary effect of the BDs. The 6MWD had a negative correlation with dyspnoea score on the diary card ($r = -0{\cdot}462$; $P < 0{\cdot}05$) and a positive correlation with mean PEF values ($r = 0{\cdot}586$; $P < 0{\cdot}01$). Post-exertional dyspnoea also had a negative correlation with PEF (VAS score $r = -0{\cdot}507$; $P < 0{\cdot}01$ Borg score $r = -0{\cdot}569$;

TABLE 1. Demographic details of participating COPD patients

| Patient | Sex | Age (years) | Mean baseline | | Drugs |
|---|---|---|---|---|---|
| | | | $FEV_1$% predicted | 6MWD | |
| GN | F | 77 | 33 | 271 | S,I , B |
| GB | M | 62 | 18 | 190 | S, A, B |
| DS | F | 63 | 24 | 280 | S |
| AWh | M | 74 | 32 | 415 | S, I, B |
| PD | F | 63 | 44 | 529 | S, A |
| IC | F | 77 | 26 | 556 | S, I, B |
| JG | F | 62 | 36 | 464 | S, I |
| DD | F | 67 | 32 | 431 | S |
| TD | M | 70 | 26 | 471 | S |
| ED | M | 71 | 44 | 634 | S, A |
| GD | M | 79 | 45 | 523 | S, I, B |
| JT | F | 75 | 31 | 395 | S, I, A, D |
| LE | M | 64 | 30 | 564 | S, I, A |
| HL | M | 65 | 29 | 466 | S, I |
| DK | M | 71 | 46 | 501 | S, B |
| AW | M | 71 | 40 | 352 | S |
| SC | F | 63 | 29 | 476 | S, I, B, A, D |
| BB | M | 57 | 32 | 533 | S, I |
| GS | F | 64 | 45 | 506 | S, I, A, B |

S: salbutamol; I: ipratropium bromide; B: beclomethazone inhaler; A: aminophylline oral; D: diuretic oral.

Table 2. Data from three clinic days

| | Active nebulized drugs (+placebo MDI) | | | | Placebo nebulized drugs (+active MDI drugs) | | | |
|---|---|---|---|---|---|---|---|---|
| | Baseline median | (range) | Post-BD median | (range) | Baseline median | (range) | Post-BD median | (range) |
| $FEV_1$ (l) | 0·78 | (0·52–1·38)**** | 1·06 | (0·6–1·84) | 0·88 | (0·46–1·42)**** | 1·08 | (0·58–1·62) |
| FVC (l) | 2·06 | (1·52–3·78)**** | 2·52 | (1·78–4·64) | 2·02 | (1·22–3·68)**** | 2·64 | (1·76–4·12) |
| SVC (l) | 2·07 | (1·62–3·82)**** | 2·46 | (1·76–4·48) | 1·80 | (1·13–3·93)**** | 2·61 | (1·43–4·48) |
| TLC (l) | 6·20 | (4·7–7·4) NS | 5·94 | (4·4–8·45) | 6·20 | (10·0–4·5) NS | 6·10 | (4·3–8·8) |
| RV (l) | 4·10 | (2·4–6·9)** | 3·40 | (2·2–5·4) | 4·00 | (2·9–6·9)*** | 3·50 | (2·3–6·1) |
| Sgaw ($s^{-1}kPa^{-1}$) | 0·23 | (0·12–0·58)**** | 0·35 | (0·13–0·80) | 0·22 | (0·13–0·56)*** | 0·32 | (0·15–0·60) |
| 6 MWD | 470 | (183–636)*** | 507 | (289–657) | 475 | (196–632)*** | 529 | (290–660) |
| VAS (mm) | 65 | (10–90)** | 51 | (9–81) | 65 | (6–95)* | 43 | (4–93) |
| Borg score | 5 | (4–6)* | 4 | (2–6) | 5 | (3–7)* | 4 | (2–7) |

Wilcoxon rank tests: *$P<0·05$; **$P<0·01$; ***$P<0·001$; ****$P<0·0001$.

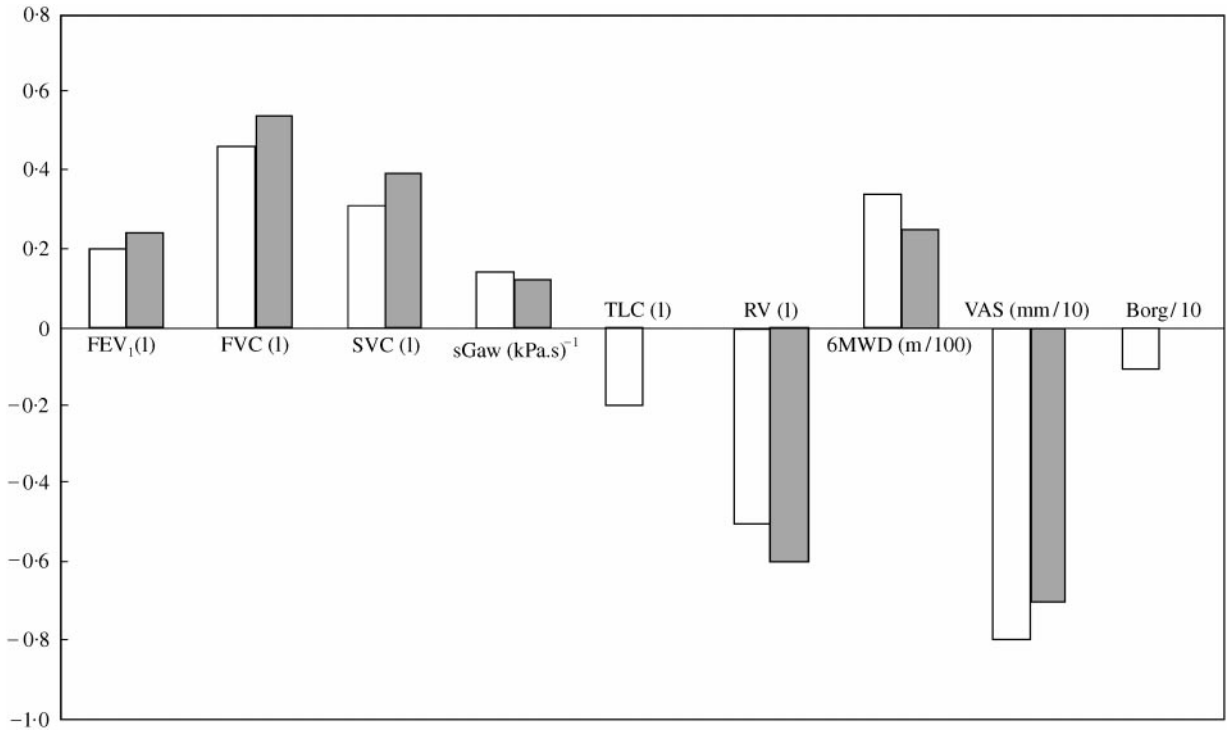


FIG. 1. Median changes in $FEV_1$, FVC, SVC, sGaw, TLC, RV, 6MWD and dyspnoea scores for 19 COPD patients. There is no significant difference between BD after nebulizer (shaded bars) and after MDI (open bars).

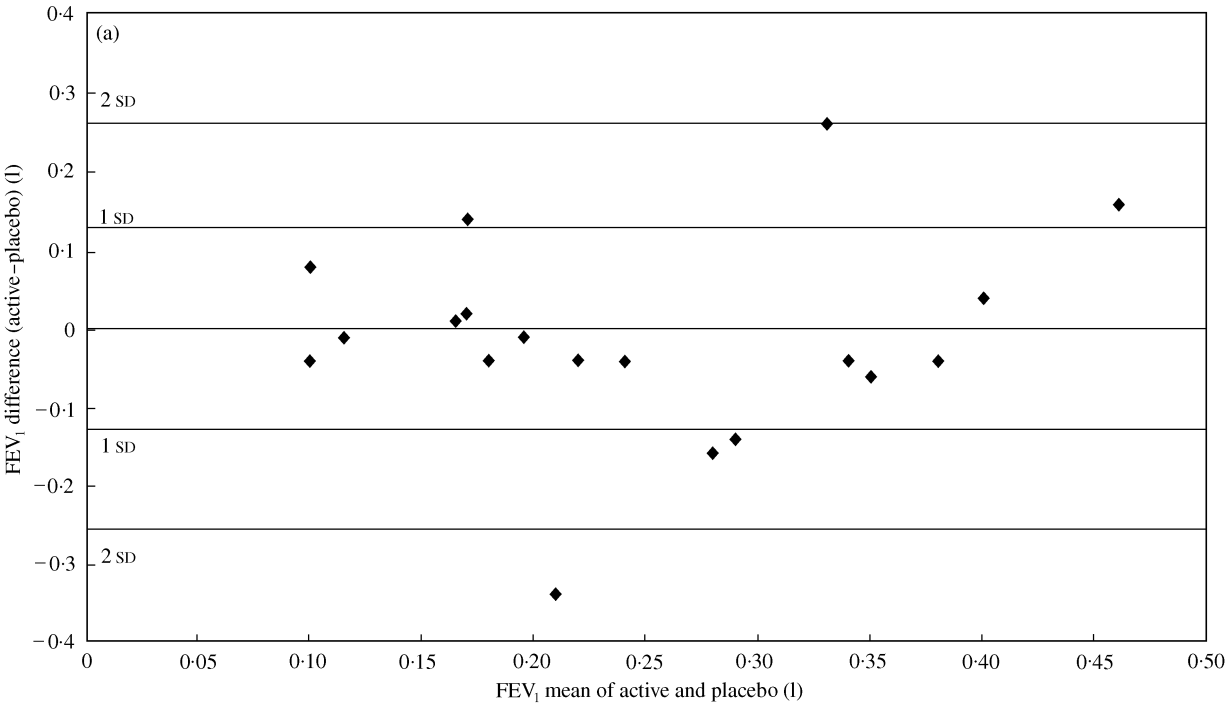


FIG. 2. Bland–Altman plots comparing individual changes after nebulized BD and BD via MDI with nebulized placebo. Mean change in (a) $FEV_1$, (b) FVC and (c) 6MWD are plotted against difference between changes.

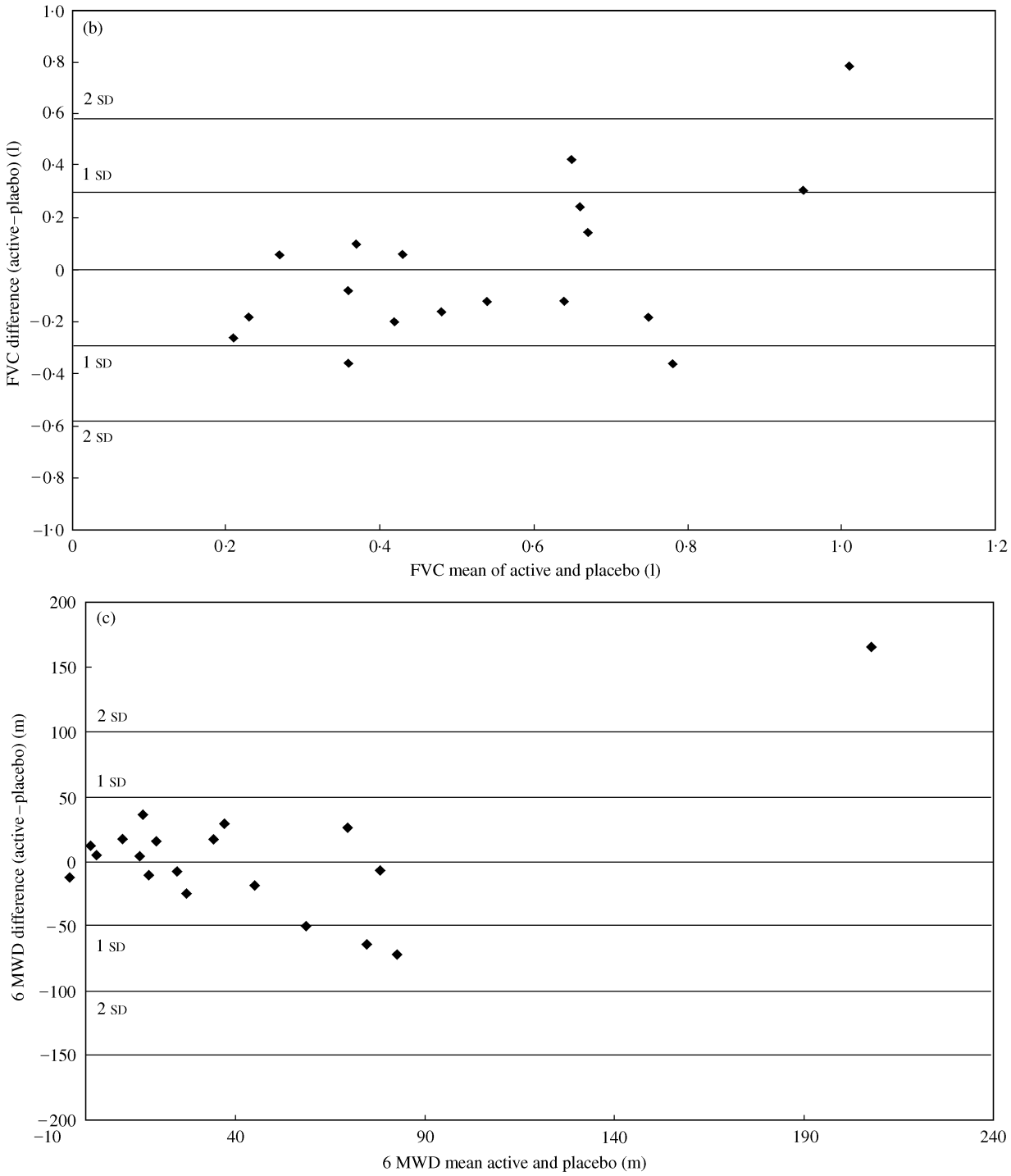


Fig. 2. (*continued*)

$P<0{\cdot}01$). In addition, FVC was positively correlated, with mean PEF scores ($r=0{\cdot}476$; $P<0{\cdot}04$) and TLC had a negative correlation with diary card scores for dyspnoea ($r$ $-0{\cdot}559$; $P<0{\cdot}01$). There were no other significant correlations between acute BD testing and domiciliary diary card results.

## Discussion

In 1980 (20) a study of five patients with severe COPD showed that, compared to placebo, nebulized salbutamol improved PEF, symptom score and rescue inhaler use and that all patients preferred active nebulized drugs. Since

Table 3. Compares diary card and questionnaire scores

| | Active nebulized drugs + placebo MDI | | | Placebo nebulized drugs + active MDI | | | Normal inhalers only | |
|---|---|---|---|---|---|---|---|---|
| | Median | Range | $P_1$ | Median | Range | $P_2$ | Median | Range |
| **Diary cards** | | | | | | | | |
| Mean PEF ($l\,min^{-1}$) | 228 | (124–325) | ** | 215 | (118–315) | ** | 209 | (123–300) |
| Dyspnoea score | 2·8 | (1·4–3·2) | | 2·6 | (1·6–3·5) | | 2·9 | (1·5–3·4) |
| Quality of life score | 2·8 | (1·2–3·2) | | 2·8 | (1·9–3·5) | ** | 2·9 | (1·5–3·4) |
| Extra puffs inhaler | 0·8 | (0–5·1) | * | 1·1 | (0–7·6) | ** | 1·6 | (0–8·7) |
| Noctural walkings | 0 | (0–2·3) | | 0·1 | (0–1·2) | | 0·2 | (0–1·4) |
| **Questionnaire scores** | | | | | | | | |
| SGRQ | | | | | | | | |
| Total | 61 | (35–79) | | 65 | (37–84) | | 64 | (34–81) |
| Symptoms | 75 | (32–100) | | 73 | (42–100) | | 73 | (34–100) |
| Activity | 79 | (60–93) | * | 86 | (54–100) | | 80 | (60–100) |
| Impact | 43 | (23–73) | | 49 | (22–80) | | 51 | (19–77) |
| StG30 | 20 | (13–28) | | 21 | (12–25) | | 21 | (11–29) |
| HAD | | | | | | | | |
| Anxiety | 8 | (1–18) | | 8 | (0–18) | | 7 | (2–18) |
| Depression | 6 | (2–15) | | 7 | (2–15) | | 6 | (2–15) |

Wilcoxon rank scores: $P_1$ compares nebulized BD and placebo; $P_2$ compares nebulized BD and MDI drugs only; no significant differences between placebo nebulized drugs + MDI and MDI only.

then, routine use of domiciliary nebulizers has dramatically increased. This is partly due to the patients' belief that nebulizers are the most effective treatment for all chest complaints and that denying them the use of nebulizers represents sub-optimal treatment, and partly because many General Practitioners recommend nebulizers without any formal BD assessment. In addition, recently patients have been able to order nebulizers via mail order catalogues.

Unfortunately, previous studies have produced conflicting recommendations regarding the most appropriate method of assessing nebulizers responses. A recent BTS publication (11) has attempted to give rational guidelines, but there is a relative paucity of double-blind, placebo-controlled trials with which to produce evidence-based recommendations. The present study is one of the few to attempt this.

## EFFECTS OF DOSE AND DEVICE

A number of studies have compared the effects of BDs inhaled from MDI (with or without spacing devices) with those from nebulizers (1–5), whilst others have studied dose–response characteristics of $\beta_2$-adrenergic stimulants and anti-cholinergic agents. The results from some of these studies have suggested that large nebulized doses of BDs confer little advantage over MDI doses to patients with stable COPD. For example, it was found that ipratropium bromide had equipotent acute effects on lung function, comparing 80 $\mu$g and 40 $\mu$g via MDI with 288 $\mu$g and 0·1 mg, respectively, via a nebulizer in patients with moderately severe COPD (1,21). In addition, Gunawardena *et al.* (2) reported that in 32 patients with severe COPD 120 $\mu$g ipratropium bromide via an MDI produced similar BD responses to 125 $\mu$g and 500 $\mu$g via a nebulizer, both acutely and also when used regularly at home.

Similar dose–response effects have been reported for $\beta_2$-adrenergic agonists in a number of other studies (22–25). Thus, the effects on spirometry, 6MWD and scores from the Chronic Respiratory Disease questionnaire of 0·5 mg, 1 mg and 1·5 mg terbutaline inhaled via an MDI were similar (22), and salbutamol rotacaps 1 mg, 2 mg and 4 mg gave similar acute spirometric responses, although the responses lasted longer with the higher doses (23). In an early study of asthmatic and normal subjects (24), terbutaline via MDI and spacer produced greater rises in $FEV_1$ and sGaw than via a nebulizer, dose for dose. A more recent, open study of 20 patients with severe COPD (25) also reported that terbutaline 2 mg via MDI with spacer gave similar improvements in $FEV_1$ and FVC to 5 mg via a nebulizer. Our study has produced similar results. The combined effects of anti-cholinergic agents and $\beta_2$-adrenergic agonists given in regular, relatively small, clinically-used doses via MDI with spacer produced similar responses to the larger doses via nebulizer, both acutely in the laboratory and at home. The most likely reasons are firstly that there may be differences in deposition of aerosol inhaled by tidal breathing from the nebulizer compared with that inhaled with maximal breaths from the MDI plus

spacer, and also that aerosol nebulized during expiration is wasted. However, our results contrast with those from studies where the effects of nebulized drugs were compared with the patients' normal medication rather than with standardized, regular MDI with spacer (8–10,29). Thus, there may be some benefit in taking regular BDs via MDI with spacer compared with an unregulated regime.

## ACUTE OR DOMICILIARY ASSESSMENT

The predictive value of acute changes in spirometry and other lung function tests has been questioned by several groups over the past few years (8–10,27) since they often correlated poorly with patients symptoms when they received their nebulizers at home. However, subjective changes may not be a reliable indicator in this situation because of the marked placebo effect often associated with nebulizer use. Jenkins *et al.* (3) reported that all 19 of their COPD patients felt better using a nebulizer rather than an MDI although there were no differences in PEF, spirometry, 6MWD, rescue inhaler use or in symptoms. Thus, the expectation of improvement may have affected the results of the large, but open, non-randomized studies reported by O'Driscoll (8,27) and Goldman (10), which reported poor correlations between acute changes in spirometry, and domiciliary diary cards and PEF. Although Goldman's patients had nebulized placebo for the first week, this was not blinded and the other two studies were not placebo-controlled. Nevertheless, the smaller study of 20 COPD patients by Teale *et al.* (9), which was double-blind and placebo-controlled, confirmed the lack of correlation between acute changes in lung function (except sGaw) and domiciliary PEF. Acute changes in exercise tolerance were not measured in this study.

Our study was also double-blind and placebo-controlled. Although most patients reported feeling better when they had a nebulizer, the diary card data did not confirm this; the period with and without nebulizer gave similar scores for all parameters. Our study showed that acute improvements in exercise tolerance, exercise-induced dyspnoea, FVC and TLC all correlated significantly, although modestly, with home increases in both perceived dyspnoea and in PEF. In our hands, therefore, acute changes in FVC and 6MWD were useful predictors of domiciliary response to BD medications in these patients. Although TLC can be used also, this is a more difficult and less reproducible measurement.

## REPRODUCIBILITY OF BD RESPONSES AND SIGNIFICANT CHANGES

A further problem with interpretation of acute BD responses is their relatively poor reproducibility (28–33) and the difficulty in deciding what constitutes a significant BD response. Because of the large within-subject variation of these responses (30,32), it has been suggested that no decision about treatment should be made on the strength of one estimation of BD response. For instance, in one study, five BD responses over a 21-month period had a within-subject standard deviation of 186 ml for $FEV_1$ (32). Similarly, an intra-subject coefficient of variation of 61% (change as percentage of baseline) and 57% (change as percentage of predicted) was found for 111 COPD patients performing six BD responses with $FEV_1$ manoeuvres over 2 years (33). This lack of reproducibility could have influenced the results from a study such as ours. An additional problem is that the reproducibility of longer-term domiciliary responses to BDs of patients with COPD is entirely unknown.

The within-subject repeatability of the measurements is also an important consideration in deciding what constitutes a significant change in lung function, exercise capacity and quality of life scores. A number of studies have addressed this problem. Both Nisar *et al.* (34) and the BTS guidelines on managing COPD (11) have suggested that a change in $FEV_1$ of 15% or 200 ml is significant, whilst Morrison (26) suggested a change in PEF of 15% or 20 ml $min^{-1}$ is considered significant. In a study of 32 stable COPD subjects, Hay *et al.* (35) found that within-subjects $FEV_1$ varied spontaneously by 140 ml and FVC by 390 ml, whilst in an even larger study, Tweedale *et al.* (31) reported spontaneous intra-subject variations in $FEV_1$ of 160 ml and in FVC of 330 ml. They concluded that a significant difference should exceed these values. As mentioned before, the majority of our patients had an increase in $FEV_1$ of 200 ml or more and in FVC of 300 ml or more. There is less data concerning the reproducibility of the 6MWD in patients with COPD. However, Hay's study (35) showed an intra-subject variability of 53 m within days and 78 m between days, while Jaeschke's results (22) suggested that a change of 30–40 m was significant. We chose to take 30 m as a significant improvement and, again, half or more of the patients achieved this following BD treatment in this study.

Unlike asthmatics, COPD patients may have little or no response to a particular BD. For instance, only 11/20 patients in Morrison's study (26) had useful responses, in the study by Nissar (34) 56/127 COPD patients did not respond to salbutamol and in Teale's study 11/20 subjects had a BD-induced increase in $FEV_1$ of only 100 ml or less. The relatively small number of positive responses in the group makes interpretation of correlations of acute and domiciliary changes impossible. As mentioned before, in our study most patients achieved significant improvements in $FEV_1$, FVC and 6MWD (Fig. 1), making statistical analysis more meaningful than in previous studies.

In this study we did not demonstrate that the nebulizer itself had any effect on perceived dyspnoea (diary card data being similar when patients took active drugs via MDI with spacer, whether or not they received placebo nebules). Thus, in these patients there was neither placebo effect from having the nebulizer nor any effect of the nebulized saline on lung function or breathlessness.

In conclusion, this placebo-controlled, double-blind study of 19 patients with stable, severe COPD has shown that salbutamol and ipratropium bromide given regularly in conventional, clinical doses by MDI associated with a spacer produce equivalent BD responses to much larger nebulized doses. Although domiciliary PEFs were statistically significantly higher on nebulized BD therapy than on

active MDI treatment, the difference was relatively small and not clinically significant. It is of note that the BTS guidelines (11) state that, compared with spirometry, PEF is not a very satisfactory measurement in COPD and perhaps should not be used to monitor progress at home. Acute assessment in our laboratory with lung function, particularly FVC and TLC, and exercise capacity proved useful predictors of longer-term outcome of treatment. Since we have found some correlation between both 6MWD and TLC with home dyspnoea scores, we suggest that either or both of these measurements could be used to assess BD responses in severe COPD.

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