

# High-dose inhaled terbutaline in the management of chronic severe asthma: comparison of wet nebulisation and tube-spacer delivery

JG PRIOR, RV NOWELL, GM COCHRANE

*From the Department of Thoracic Medicine, New Cross Hospital, and Respiratory Medicine, Guy's Hospital, London*

**ABSTRACT** Eight patients with chronic severe asthma, poorly controlled by conventional doses of inhaled bronchodilator, were treated with high-dose inhaled terbutaline (4 mg four times daily), via either wet nebulisation of terbutaline respirator solution, or by tube-spacer aerosol, using cannisters delivering 1 mg terbutaline per metered dose. All patients improved objectively and subjectively on these higher dosage regimens during both day and night. A trial of high-dose inhaled beta<sub>2</sub> sympathomimetic therapy should be considered in any patient with chronic severe asthma who fails to obtain benefit from standard doses of inhaled bronchodilator.

Patients with chronic severe asthma often respond poorly to inhaled bronchodilators in conventional dosage. Such patients are usually very disabled, require frequent hospital admissions, and are commonly prescribed long-term oral corticosteroids. Domiciliary high-dose inhaled bronchodilator therapy, delivered by wet nebulisation, may improve some patients with chronic asthma sufficiently for oral steroids to be discontinued.<sup>1</sup> However, the air compressors necessary for the domiciliary nebulisation of bronchodilator are expensive and inconvenient. We decided, therefore, to compare the efficacy of high-dose bronchodilator therapy delivered by wet nebulisation and by a new aerosol device, the tube-spacer.<sup>2</sup> The tube-spacer was chosen because it achieves higher penetration of aerosol into the lung than does conventional aerosol,<sup>3</sup> and also because it may be more effective than conventional aerosol in the management of some patients with asthma.<sup>4-6</sup> The tube-spacer is cheaper and more convenient than the wet nebuliser.

## Methods

Eight patients (four male and four female) with chronic severe asthma participated in the study. Mean first second forced expired volume (FEV<sub>1</sub>) was 0.83 l BTPS (range 0.5-1.6 l BTPS). Average age

was 60 years (range 53-67 years). Before the study started, diurnal variation of peak expiratory flow rate (PEFR) was documented by home-monitoring of PEFR, using the mini-Wright peak flow meter.<sup>7</sup> All patients showed 15% or more diurnal variation in PEFR either spontaneously or after bronchodilator. Four patients were receiving oral prednisolone (dose range 10-15 mg per day). All patients were being treated with inhaled salbutamol 200-400 µg four times daily, and (in those not taking oral corticosteroids) beclomethasone dipropionate 200-400 µg four times daily. No patient had evidence of cardiac disease. All were non-smokers. Four patients used their inhalers correctly, two used Rotahalers, and two were considered to have poor inhaler technique. Each patient understood the aim of the study, and was instructed to obtain medical advice immediately if asthma suddenly worsened.

The bronchodilator used was terbutaline. A pressurised aerosol containing 1 mg per metered dose terbutaline (four times the normal dose) was supplied. Before the study began, cumulative dose-response curves were constructed (using inhaled terbutaline 1 mg at 30-minute intervals to a cumulative maximum of 5 mg, and measuring changes in PEFR, FEV<sub>1</sub>, and vital capacity). Maximal responses in the patients occurred between cumulative doses of 2-5 mg with little further improvement after 4 mg. Studies of duration of action were not performed. The dose of terbutaline chosen for the trial was 4 mg six-hourly.

Address for reprint requests: Dr JG Prior, Chest Clinic, New Cross Hospital, Avonley Road, London SE14 5ER.

The trial consisted of three phases, each lasting two weeks, and was of "open" design. The patients were instructed in the use of the mini-Wright peak flow meter, and asked to record PEFR (best of three attempts) on waking and on retiring to bed. (This measurement was made before bronchodilator therapy, since the study was designed to examine the prophylactic effect of bronchodilator on airflow obstruction and symptoms rather than maximal bronchodilator effect.) Patients were asked to record a "symptom score" (table) for the day and night period. This was performed before PEFR measurements. Diary cards were provided to record this information.

Table Scoring system for nocturnal and daytime symptoms

Symptoms	Score
<i>Nocturnal symptoms</i>	
No cough/whoeze	0
Slight cough/whoeze	1
Woken > 3 because of cough/whoeze	2
Frequent cough/whoeze	3
<i>Daytime symptoms</i>	
No cough/whoeze	0
Occasional cough/whoeze	1
Frequent cough/whoeze	2
Severe, persistent cough/whoeze	3

During phase 1 (two-week "run-in" period) patients took their usual medication, and recorded PEFR and symptom scores. The second and third phases were of randomised crossover design between wet nebulisation and tube-spacer delivery methods for terbutaline. Terbutaline 4 mg (0.4 ml terbutaline respirator solution in 1 ml sterile water) was inhaled four times daily from the wet nebuliser using a RTU4 Medic Aid Compressor which delivers about 16% of the dose placed within the nebuliser; approximately 80% of the particles delivered are less than 7 µm diameter and 60% of the particles are within the 1-4 µm range. The same dose of terbutaline (4 mg four times daily) was inhaled from a tube-spacer. PEFR and symptom scores were recorded as before.

During phases 2 and 3, usual bronchodilator aerosol therapy was omitted, but no other change was made in treatment.

Patients were asked to record any side-effects and were informed that some of these could be irritability, hand tremor, or cramp.

PEFR values and symptom scores in each subject were averaged over each phase, and paired *t* tests were used to assess differences between the phases.

Results

Figure 1 shows mean PEFR values, and fig 2 mean symptom scores during each phase of the trial for each patient. Both morning and evening PEFR improved significantly over control values when patients were being treated with high-dose inhaled terbutaline via nebuliser or tube-spacer (*p* < 0.005). There was no overall statistically significant difference between nebuliser and tube-spacer methods of delivery, but one patient (patient 2) showed a considerably better response to inhaled terbutaline via nebuliser than via tube-spacer. Night and day symptom scores were significantly better during treatment phases with high-dose terbutaline via either nebuliser or tube-spacer, than during the control period (*p* < 0.02). There was no significant difference between nebuliser or tube-spacer delivery methods. Again, patient 2 showed greater improvement in symptom scores on nebulised terbutaline than on tube-spacer delivery of terbutaline.

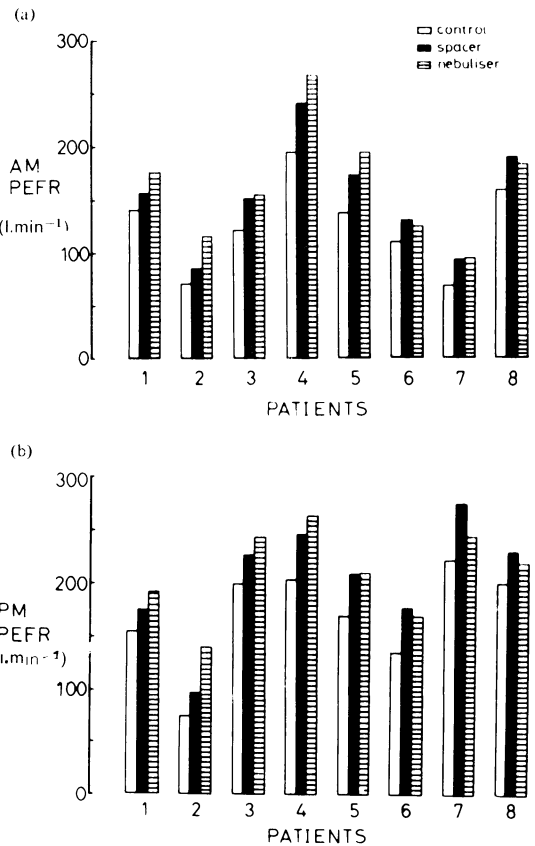


Fig 1 Average PEFR for each two-week phase for each patient—(a) average morning PEFR, (b) average evening PEFR.

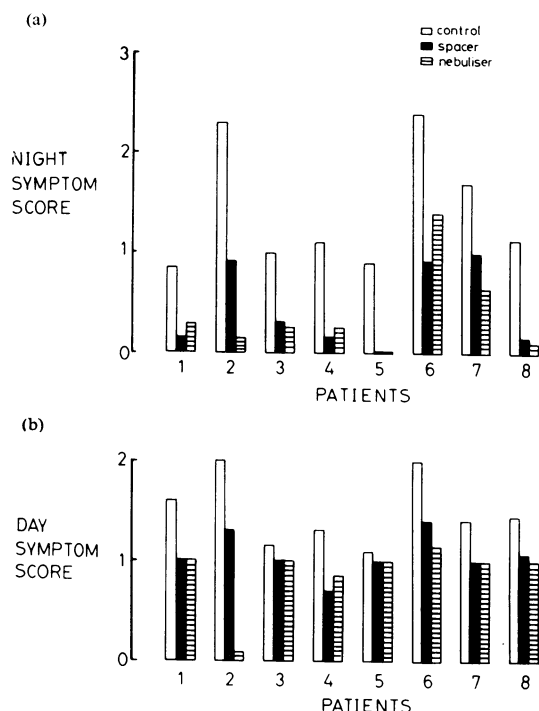


Fig 2 Average symptom scores for each two-week phase for each patient—(a) average nocturnal symptom scores, (b) average daytime symptom scores.

Night symptom scores tended to improve more than daytime scores during therapy with high dose terbutaline via both nebuliser and tube-spacer. No patient reported any side-effects while on high dose terbutaline therapy.

## Discussion

This study confirms the observations of others<sup>1 8</sup> that patients with chronic asthma may be undertreated with conventional doses of inhaled bronchodilator. Our findings that the tube-spacer delivery method was as effective in improving symptoms and PEFR as wet nebulisation in seven out of the eight patients are important, since the tube-spacer is considerably cheaper and more convenient for domiciliary use than the wet nebuliser. We cannot be certain whether the improvement in each patient was attributable to the larger dose of bronchodilator delivered, the method of delivery or a combination of both factors. Although the tube-spacer allows greater delivery of bronchodilator to the bronchial tree than does conventional pressurised aerosol,<sup>3</sup> an equivalent dose of bronchodilator delivered by pressurised aerosol or Rotahaler might

be as effective as nebuliser or tube-spacer.

A feature of this study was the degree of improvement in nocturnal symptoms in patients on high dose terbutaline. The duration of bronchodilator activity is related to the inhaled dose.<sup>9</sup> A higher dose of inhaled bronchodilator at bed time should be more effective in the prophylaxis of nocturnal bronchoconstriction and symptoms than a standard dose. Better daytime control of asthma might also improve nocturnal symptoms. Raising bed time PEFR by better daytime control of asthma could therefore exert a prophylactic effect on nocturnal cough and wheeze.

At present, the only convenient delivery method for high-dose inhaled bronchodilator therapy is the pressure-driven nebuliser employing respirator solutions. Simpler and cheaper high dose bronchodilator delivery systems (high-dose inhaler or Rotahaler) would be desirable. However, many physicians are still reluctant to use<sup>10</sup> and drug companies reluctant to advise higher doses of inhaled bronchodilator when conventional doses do not achieve adequate control of symptoms. This may reflect the epidemic of asthma deaths in 1960s associated with the apparent excessive use of inhalers.<sup>11</sup> Provided that patients on high-dose inhaled beta<sub>2</sub> stimulants are instructed to obtain immediate medical advice should their asthma suddenly deteriorate, such therapy appears to be safe, and the lack of side-effects or toxicity in our patients on high dose inhaled terbutaline supports this view.

Patients with chronic severe asthma should be given a trial of high-dose inhaled bronchodilator therapy. While wet nebulisation is the only practical delivery method available at present, our study has shown that cheaper and more convenient methods of high-dose bronchodilator aerosol delivery can be just as effective as wet nebulisation.

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