Regular nebulised terbutaline in chronic obstructive airways disease: dose-response studies fail to detect tolerance

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- 1 To determine the effects of high dose terbutaline on the possible development of tolerance we have examined the influence on dose-response of regular nebulised terbutaline.
- 2 We studied 10 subjects with severe chronic obstructive airways disease (COAD), mean age 63 years mean (s.e mean) PEFR 142 l min⁻¹ (19), FEV₁ 0.77 l (0.12) and FVC 1.93 l (0.19). Cumulative dose-response curves were measured (PEFR, FEV₁ and FVC) to six incremental doses of terbutaline (0.5–8 mg) before and 1, 4, 8 and 12 weeks after starting nebulised terbutaline 5 mg four times a day.
- 3 Maximal bronchodilatation (E_{max}) was calculated by polynomial regression. Responses were examined by analysis of variance.
- 4 Mean baseline PEFR increased by 32 l min⁻¹ ($P < 0.05$), FEV₁ by 0.16 l (NS) and FVC by 0.54 l ($P < 0.05$) after 12 weeks. Initial mean E_{max} PEFR was maintained throughout the study. The percentage of mean E_{max} PEFR achieved by each cumulative dose of terbutaline either increased (0.5 mg, 1 mg and 2 mg, $P < 0.01$) or was maintained (4 mg, 6 mg and 8 mg) throughout the study.
- 5 We conclude that in severe COAD regular nebulised terbutaline 5 mg four times a day produces a sustained improvement in baseline lung function without changes in dose-response which would suggest tolerance.

Keywords nebulise terbutaline tolerance chronic obstructive airways disease

Introduction

Increasing doses of inhaled β_2 -adrenoceptor agonists have been shown to produce further bronchodilatation in asthma (Barnes & Pride, 1983; Lipworth *et al.*, 1988; Nelson *et al.*, 1983; Prior & Cochrane, 1982) and chronic obstructive airways disease (COAD) (Corris *et al.*, 1983; Vathenan *et al.*, 1988a) and regular nebulised bronchodilators have been shown to improve home PEFR in COAD (O'Driscoll *et al.*, 1990). However concerns remain over side effects (Harvey *et al.*, 1981) and the possible development of tolerance. The question of tolerance to β_2 -adrenoceptor agonists has been extensively studied with clear evidence of tolerance as regards heart rate (Barnes and Pride, 1983), metabolic responses (Harvey & Tattersfield, 1982; Jenne *et al.*, 1977), tremor (Prior & Cochrane, 1982) and bronchodilator effects in normal subjects (Larsson *et al.*, 1977), but the majority of studies have failed to detect evidence of bronchodilator tolerance in asthma (Larsson *et al.*, 1977; Nelson *et al.*, 1983; Tattersfield, 1985).

Few studies have examined the question of bronchodilator tolerance to high dose nebulised β_2 -adrenoceptor agonists; only one has been published as a full paper and failed to detect tolerance to a modest dose of terbutaline, 5 mg twice a day (McGivern *et al.*, 1984). To clarify the long term effects of nebulised bronchodilators we have examined dose-response curves in 10 subjects with COAD to look for baseline changes and the possible development of tolerance.

Methods

We studied 10 patients with stable COAD all of whom had less than 20% increase in FEV₁ after terbutaline 0.5 mg by Turbohaler but more than 20% response to terbutaline 8 mg, and all of whose maintenance therapy had been stable for at least 1 month (details shown in Table 1).

All studies were performed at 14.00 h with inhaled bronchodilators omitted for at least 6 h and oral bronchodilators at least 48 h before each study session. Peak flow was measured using a Wrights peak flow meter (best of three) and FEV₁ and FVC with a dry wedge spirometer (Vitalograph) using the largest of three reproducible curves. Baseline PEFR, FEV₁ and FVC were recorded and subjects were then given terbutaline 0.5 mg by Turbohaler with spirometry and PEFR measured 15 min later. Turbohaler usage was supervised and all subjects had a satisfactory technique. The procedure was repeated with increasing doses of terbutaline to give six cumulative doses of terbutaline 0.5, 1, 2, 4, 6 and 8 mg.

Subjects were then issued with a home nebuliser (Micro neb III, Lifecare) and prescribed terbutaline 5 mg four times a day. Dose-response curves were repeated 1, 4, 8 and 12 weeks after starting nebulised terbutaline. In addition full lung volumes were measured before starting and after 12 weeks on nebulised terbutaline. Vital capacity and total lung capacity (helium) were measured with a helium residual volume apparatus (Warren and Collins) and other lung volumes with a Gould 2800 autobox plethysmograph. Patients were questioned regarding their nebuliser usage at each assessment visit but there was no independent check on compliance. Home PEFR measurements were not assessed. Patients were withdrawn from the study if other treatment was changed. A placebo controlled study was not considered to be appropriate on ethical grounds as will be discussed later.

Statistical analysis

Changes in baseline PEFR, FEV₁, FVC and lung volumes were examined by analysis of variance (ANOVAR) and further pairwise comparisons using Fisher's least significant difference. To avoid the complicating effects of baseline changes on the detection of tolerance we used polynomial regression to calculate maximal bronchodilatation (E_{max}) for each dose response curve and then the mean E_{max} PEFR and the mean percentage of E_{max} PEFR achieved with each cumulative dose of terbutaline. Changes in mean E_{max} PEFR and %E_{max} PEFR achieved with each cumulative dose of terbutaline were examined by ANOVAR.

Results

Details on the 10 subjects completing the study are shown in Table 1; they had a mean baseline FEV₁ of 0.77 l (range 0.54–1.65 L), a mean baseline FEV₁ % predicted 34% (range 22–52%) and a mean age of 63 years (range 44–76 years). Only two gave a history of atopy. Three had physiological evidence of emphysema and two fulfilled the Medical Research Council (MRC) criteria for mucus hypersecretion. One further subject was withdrawn after 6 weeks of nebuliser therapy following an acute exacerbation.

Table 2 shows the mean baseline PEFR, FEV₁ and FVC. ANOVAR applied as an overall significance test to the change in baseline after starting nebulised terbutaline showed a significant time effect for PEFR and

Table 1 Patient details

Age/Sex (years)	Years disease	Atopy	Smoker (pack years)	Medication	FEV ₁ (l)	(% predicted)
1 63 M	7	—	—	IB, IS, T	0.71	32%
2 75 M	12	—	—	IB, OB, IS	0.60	33%
3 72 M	50	+	—	IB, IA, IS, T	1.18	52%
4 59 M	12	—	—	IB, IA, I/OS, T	0.76	29%
5 54 F	10	+	18	IB, IA, I/OS, T	0.73	27%
6 44 M	5	—	14	IB, IA, IS	1.65	48%
7 59 M	20	—	26	IB, IA, IS	0.83	25%
8 61 M	40	—	—	IB, IA, IS, T	0.55	22%
9 76 F	4	—	—	IB, IA, IS	0.69	46%
10 61 F	5	—	—	IB, IA, IS, T	0.54	28%
63					0.77	34%

Medication IB = Inhaled β_2 -adrenoceptor-agonist
 IA = Inhaled anti-cholinergic
 IS = Inhaled steroid
 OS = Oral steroid
 T = Oral theophylline.

Table 2 Baseline PEFR (l min⁻¹), FEV₁ (l) and FVC (l) before and after 1–12 weeks on nebulised terbutaline (means 10 subjects (s.e. mean))

	Time on nebulised terbutaline 5 mg four times daily				
	Baseline	1 week	4 weeks	8 weeks	12 weeks
FEV ₁	0.77 (0.12)	0.87 (0.11)	0.91 (0.14)	0.94 (0.14)	0.93 (0.16)
FVC	1.93 (0.19)	2.27 (0.20)	2.30 (0.28)	2.43 (0.27)	2.47 (0.27)
PEFR	142 (19)	170 (24)	172 (24)	182 (27)	174 (22)

FVC ($P < 0.05$) but not FEV₁. Further pairwise comparisons using Fishers least significant difference indicated that for all variables there was a significant difference between baseline and weeks 1, 4, 8 and 12 respectively but no subsequent significant difference between any of weeks 1, 4, 8 and 12. The subject who was withdrawn showed a similar pattern of response with an improvement in baseline after 1 week of nebulised terbutaline which was maintained at 4 weeks.

Table 3 shows lung volumes before starting and after 12 weeks on nebulised terbutaline. Although small improvements can be seen in most parameters ANOVA failed to detect a significant overall change in lung volumes.

Table 4 shows the mean $E_{\max}$ PEFR achieved at each visit and the mean % $E_{\max}$ PEFR achieved with each cumulative dose of terbutaline (0.5 mg to 8 mg) at each visit. It can be seen that baseline mean $E_{\max}$ PEFR was 208 l min⁻¹; the small subsequent increases in mean $E_{\max}$ PEFR, up to 219 l min⁻¹ at 12 weeks were not significant. Initially terbutaline 0.5 to 8 mg produced from 75% to 100% of mean $E_{\max}$ PEFR. ANOVA showed a highly significant improvement in the subsequent responses to 0.5 mg, 1 mg and 2 mg ($P < 0.01$) although the small changes in response to higher doses of terbutaline failed to achieve significance at the 1% level. Had subjects exhibited tolerance we would have expected to see a fall in baseline lung function and/or a fall in the percentage of $E_{\max}$ achieved with a given dose of terbutaline. In fact baseline lung function rose with no decrease in response to terbutaline suggesting tolerance did not develop.

Discussion

Our results suggest that in severe COAD treatment with nebulised terbutaline 5 mg four times a day for 12 weeks

leads to improvements in baseline lung function without evidence of tolerance detectable by changes in dose-response curves.

Three previous studies, two of which were published in abstract form only, have looked for evidence of tolerance to high dose nebulised β_2 -adrenoceptor agonists. Stainforth & Tattersfield (1983) (abstract) showed slight reduction in bronchodilator response to salbutamol after 2 months of nebulised salbutamol 5 mg three times a day suggesting possible tolerance. In contrast McGivern *et al.* (1984) studied dose-responses in six asthmatics after 1 month of terbutaline 5 mg twice a day and found no evidence of tolerance; our results using higher doses of terbutaline over 12 weeks agree with their findings. Higgs *et al.* (1984) also failed to detect tolerance in 20 subjects with COAD three and six months after starting terbutaline 5 mg four times daily.

A number of points need to be considered in assessing our results. Firstly our study, like all others which have been performed, was not placebo controlled. All our patients had severe symptoms and a documented response of $> 20\%$ to high but not low dose inhaled terbutaline; as such we felt that to deny them active treatment by randomising them to placebo for the 12 weeks of the trial would be unethical. Secondly, one patient was withdrawn following an acute exacerbation. A study of patients with severe airflow limitation such as this is likely to have drop outs and the exclusion of such patients who have done badly may bias the results. Our one drop out had a similar response to the rest of the group until his acute exacerbation. Thirdly, the improvement in baseline FEV₁ of 100 ml seen after 1 week of nebulised terbutaline was less than that required to exceed natural variability with 95% confidence. However, the improvement in FEV₁ of 160 ml at 12 weeks does achieve this level of response as does the increase in FVC of 340 ml at 1 week (Tweedale *et al.*, 1987). Finally, in a study of only 10 patients our failure to detect tolerance may be due to a type 2 error. However, our finding of highly significant increases in response to the lower doses of terbutaline (0.5 mg, 1 mg and 2 mg), which are probably the most sensitive to changes in the dose-response curve, is against such a possibility.

The improvements in baseline PEFR and spirometry after 1 week on nebulised terbutaline must be due, at least in part, to the longer duration of action of nebulised terbutaline causing residual effects even more than 6 h after the last dose. The maintenance of this improvement at 12 weeks provides further evidence that tolerance did

Table 3 Lung volumes before and after 12 weeks on nebulised terbutaline. Means 10 subjects (s.d.)

		Time on nebulised terbutaline	
		Baseline	12 weeks
VC	(l)	2.1 (0.7)	2.4 (0.8)
TLC Box	(l)	7.7 (1.9)	7.3 (1.1)
TLC He	(l)	5.2 (1.1)	5.4 (1.2)
FRC	(l)	6.0 (2.0)	5.4 (1.5)
RV	(l)	5.3 (1.9)	4.5 (1.3)

Table 4 Maximal PEFR bronchodilatation ($E_{\max}$) and % $E_{\max}$ PEFR achieved with terbutaline 0.5 to 8 mg before and after starting nebulised terbutaline 5 mg four times daily. Means 10 subjects (s.e. mean)

		Time on nebulised terbutaline (T)				
		Baseline	1 week	4 weeks	8 weeks	12 weeks
$E_{\max}$ PEFR (l min ⁻¹)		208 (23)	218 (27)	224 (27)	212 (29)	219 (34)
% $E_{\max}$	0.5 mg T	75 (2.3)	85 (3.5)	86 (2.4)	91 (2.4)	85 (2.2)
% $E_{\max}$	1 mg T	83 (2.5)	89 (2.5)	91 (1.6)	94 (2.3)	89 (1.4)
% $E_{\max}$	2 mg T	87 (1.4)	90 (2.1)	95 (1.3)	96 (2.3)	95 (1.6)
% $E_{\max}$	4 mg T	97 (1.2)	93 (2.8)	100 (2.9)	99 (1.3)	99 (1.8)
% $E_{\max}$	6 mg T	99 (1.1)	93 (2.9)	102 (2.5)	101 (1.8)	102 (1.1)
% $E_{\max}$	8 mg T	100 (1.4)	102 (1.2)	102 (1.4)	103 (1.4)	101 (0.5)

not develop. Improvement in baseline on nebulised terbutaline was reported by McGivern *et al.* (1984) but not Higgs *et al.* (1984). The observation that baseline changes occur within the first week of nebuliser therapy may have implications for the design of 'nebuliser trials'. Recent studies have suggested that home recording of PEFR may be the most appropriate objective assessment of response to a home nebuliser (O'Driscoll *et al.*, 1990; Teale *et al.*, 1990) but the most appropriate duration of measurement of PEFR at home is not known. Our results suggest that a 1 week period of measurement may be adequate although this requires confirmation as the results of single laboratory measurements of PEFR may differ from those of multiple recordings of PEFR at home.

Our failure to detect a significant fall in lung volumes is perhaps surprising particularly as reduced gas trapping is thought to contribute to patient's response to home nebulisers. This could have been due to a type 2 error and in fact paired *t*-tests, which should be interpreted with caution given the number of parameters screened, showed a significant fall in TLC box ($P < 0.05$).

Analysis of the dose-response curves not only failed to detect evidence of tolerance, but in fact showed an increased response to the lower doses of terbutaline. This increased response may be due to baseline bronchodilatation allowing improved drug access to distal receptors.

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