Aminophylline and mucociliary clearance in patients with irreversible airflow limitation

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Were aminophylline to improve mucociliary function, it might prove useful in the management of irreversible airflow limitation. Eight subjects with irreversible airflow limitation due to emphysema inhaled an aerosol of ^{99m}Tc sulphur-colloid particles on each of 2 days. On day 1 aminophylline was administered intravenously, while on the other nothing was given. Particle clearance was measured by recording posterior gamma-camera images sequentially over a 24 h period. No significant differences were recorded between aminophylline and control studies, but there were marked variations in clearance between study days and between individuals. These differences were compatible with the known effects of airways obstruction and breathing pattern on the sites of particle deposition within the bronchial tree. The latter factors appeared to exert a far greater influence on the observed mucociliary clearance than did aminophylline.

Keywords aminophylline mucociliary clearance particle deposition

Introduction

Three recent studies (Sutton *et al.*, 1981; Matthys *et al.*, 1983; Schmidt *et al.*, 1983) have suggested that theophylline may share with β -adrenoceptor agonists the ability to improve mucociliary clearance within the airways, which, if so, might provide a rationale for theophylline therapy in the presence of irreversible airflow limitation. However, the study population in all three was limited and the subjects had varying degrees of reversible airflow limitation. Moreover, the investigators appear not to have taken into account the effects of these factors on the site of deposition and consequently on mucociliary clearance (Pavia *et al.*, 1980). We elected to study the effect of intravenous aminophylline on tracheo-bronchial particle clearance in patients with severe irreversible airflow limitation.

Methods

Eight male subjects with severe emphysema were studied. All had smoked heavily but only three were current smokers. All had severe airflow limitation (mean FEV_1 of 29% predicted). None had shown a 5% improvement in FEV_1 with 5 mg inhaled salbutamol or to a combination of inhaled β -adrenoceptor agonists and oral theophylline. Five had also failed to respond to oral prednisone. The project was approved by the Health Sciences Standing Committee of Human Research of the University of Western Ontario.

The study took place in two parts, performed in random order, on two separate days within the same week. All theophylline preparations were withdrawn for 48 h and all inhaled bronchodilators for 12 h before the study. On day 1 the

subject received an intravenous infusion of aminophylline as a loading dose ($6 \text{ mg kg}^{-1} \text{ min}^{-1}$) over 45 min followed by a maintenance dose ($0.9 \text{ mg kg}^{-1} \text{ min}^{-1}$) for 4 h during the study. No drug was given on the second day. All had their ventilatory capacity assessed in the immediate 24 h before being given the aminophylline infusion and again shortly after the first imaging.

The aerosol imaging techniques for the lung have been fully described elsewhere (Chamberlain *et al.*, 1983). Briefly, a $^{99\text{m}}\text{Tc}$ sulphur-colloid aerosol, containing particles of mass mean diameter $0.78 \mu\text{m}$ and GSD 1.3 which are stable for over 24 h, was administered via a mouthpiece whilst the subject breathed tidally in the sitting position. The total radioactive burden did not exceed 2 mCi (75 MBq). Posterior images were recorded with a gamma camera immediately and at 1, 3, 5–6, 7–8 and 24 h afterwards using skin markers to facilitate subsequent computer analysis. The stored images were analysed for the total counts in the lungs corrected for radioactive decay and expressed as a percentage of initial deposition. The amount cleared in 24 h was assumed to represent tracheobronchial deposition. A further index of tracheobronchial to alveolar deposition was recorded from the initial scan using central and peripheral zones.

Each subject's rate of tracheobronchial clearance was calculated assuming an exponential pattern and expressed as the clearance half-life. Statistical differences between the data pairs at each time were assessed with the Wilcoxon signed rank test and the relation between variables using linear regressions.

Results

The mean clearance curves, with and without aminophylline, are illustrated in Figure 1 and are similar to all time points. Within these mean values there was a wide range of both inter- and intra-subject differences both as to clearance and for the depth of penetration of the particles into the bronchial tree. The expected linear relationship (Pavia *et al.*, 1976) between the percent of particles remaining at 24 h (alveolar deposition) and FEV_1 was significant in the control studies ($r = 0.75$, $P < 0.01$) but not in the aminophylline studies ($r = 0.49$). Alveolar deposition and the peripheral to central deposition ratio correlated well for both study days ($r = 0.79$, $P < 0.01$).

Initially three subjects appeared to have improved tracheobronchial clearance with aminophylline whilst two were unchanged and three were worse (Table 1). Some of this

Figure 1 Mean percentage of initial counts retained in the lungs (± 1 s.e. mean) during control (●) and aminophylline (x) studies. Values are all corrected for natural radioactive decay.

variability is explained by a significant linear correlation between the 24 h retention and the clearance half-life ($\% 24 \text{ h retention} = 2.11 \times \text{half-life} + 49.4$, $r = +0.49$, $P < 0.05$) i.e. the further the particles penetrate into the lungs, the longer it takes to clear them.

Two subjects experienced side-effects from the aminophylline in the form of increased respiratory rates (24 to 28 min^{-1}) and a further two complained of nausea. In these same two subjects, satisfactory post-infusion spiromgrams could not be obtained, while in the remainder the mean change in the FEV_1 was not significant, i.e. $+3.7\%$ (range -4 – $+7\%$).

Discussion

Particles are cleared from the tracheobronchial tree by both mucociliary action and by coughing. It is impracticable to control either coughing or breathing patterns in emphysematous subjects which may explain some of the inter- and intra-subject variability observed. The expected relationship between the percentage of particles deposited in the bronchi and the FEV_1 was not statistically significant for the aminophylline studies which might have been the result of either a change in FEV_1 or in the pattern of breathing during inhalation. All our subjects had severe emphysema with irreversible airflow limitation and since response to aminophylline largely parallels the response to β -adrenoceptor agonists (Alexander *et al.*, 1980) it is most unlikely that any change in FEV_1 occurred. Breathing patterns were certainly altered clinically in two subjects and the observed tachypnoea could have led to more proximal particle deposition and thus an apparent improvement in clearance.

Table 1 Patient details and clearance half-life

Patient	Age (years)	Smoking (pack years)	FVC (l)	FEV ₁ (l)	Clearance half-life (h) Aminophylline Control	
1	72	45 (stopped 1 month)	2.6 (75)	1.2 (51)	4.2	3.0
2	71	60 (stopped 15 years)	2.5 (60)	0.9 (32)	5.9	7.5
3	77	40	2.5 (62)	0.8 (31)	9.9	12.3
4	79	45	3.2 (74)	1.3 (42)	14.3	4.3
5	45	56	2.5 (45)	0.8 (21)	8.4	8.1
6	64	100 (stopped 3 years)	1.9 (46)	0.6 (21)	8.1	6.1
7	68	60 (stopped 10 years)	2.0 (45)	0.6 (20)	8.0	8.1
8	62	94 (stopped 2 months)	1.8 (43)	0.4 (16)	3.8	4.1
Mean $\pm$ 1 s.d.			56% $\pm$ 13	29% $\pm$ 12	7.8 $\pm$ 3.3	6.8 $\pm$ 3.0

The earlier reports included subjects with some degree of reversible airflow obstruction but did not analyse their data to exclude an effect due to different patterns of particle deposition. The somewhat tenuous significance levels claimed for their paired *t*-tests become suspect when such allowances are made. Moreover, the standard errors illustrated in the study of Sutton *et al.* (1983) are of similar magnitude to our own suggesting similar variability. A further explanation for the observed variability may be that this method of measuring mucociliary clearance may be inadequate. In patients with severe disease, clearance is slow and occurs not only in the thin film of the mucociliary escalator, but also as boluses of sputum, clearance of which is affected

by both gravity and coughing. Clearance of such boluses may have a very different timecourse from particles on the mucus film that is propelled by cilia.

Our results have not demonstrated a clinically important effect of aminophylline on mucociliary clearance and, moreover, suggest that the standard method of estimating clearance needs to be interpreted with great caution. It is unwise to attribute improved clearance to a drug or intervention unless the improvement is sufficiently large to dwarf the several other factors influencing tracheobronchial clearance.

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