

# Difference in pulmonary absorption of inhaled terbutaline in healthy smokers and non-smokers

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## Abstract

**Pathophysiological studies have shown that the alveolocapillary transfer of small solutes is much faster in healthy smokers than in non-smokers. The effects of smoking on the pulmonary absorption of inhaled terbutaline were examined in normal subjects. Nine healthy smokers and 13 healthy non-smokers inhaled nebulised terbutaline and dry terbutaline powder on two study days. Plasma concentrations of terbutaline were measured up to 240 minutes after the inhalation. The plasma concentration of terbutaline rose much faster in smokers than in non-smokers, the mean time to peak terbutaline concentration being 17 minutes in the smokers and 50 minutes in the non-smokers. The peak plasma concentration was nearly twice as high in the smokers as in the non-smokers, being 21 mmol/l and 23 mmol/l for the dry powder inhalation and nebuliser respectively in the smokers and 12 mmol/l and 14 mmol/l in the non-smokers. It is concluded that smoking increases the rate of terbutaline absorption and the peak plasma concentration achieved. The rapid pulmonary absorption of terbutaline in smokers may affect the onset of action of the drug and the duration of its therapeutic effects.**

The transfer of small water soluble molecules from the alveoli to the blood has been studied extensively during the last decade to assess the functional integrity of the alveolocapillary barrier.<sup>1</sup> The radiolabelled tracer molecule technetium-99m diethylenetriamine penta-acetic acid (<sup>99m</sup>Tc DTPA) is administered in aerosol form and the radioactivity monitored over the chest, to provide a measure of the pulmonary clearance of the tracer—that is, its rate of absorption from the lung. Several groups have confirmed the findings of Jones *et al*<sup>2</sup> that the pulmonary clearance of <sup>99m</sup>Tc DTPA is much faster in healthy smokers than in non-smoking control subjects.<sup>3-6</sup>

The difference in absorption of inhaled <sup>99m</sup>Tc DTPA between smokers and non-smokers reflects a difference in the functioning of the alveolocapillary barrier, and this may affect the absorption of inhaled drugs. Most selective beta agonists are water soluble and they are frequently given by inhalation so that a high tissue concentration can be achieved in the lung. Differences in the rate of absorption

between smokers and non-smokers may affect the time course of the therapeutic effect and may be clinically relevant. The purpose of this study was to examine the effect of smoking on the pulmonary absorption of inhaled terbutaline in normal subjects, and its relation to the pulmonary clearance of <sup>99m</sup>Tc DTPA.

## Methods

### SUBJECTS

We studied 22 healthy men, nine smokers and 13 non-smokers. None of the smokers had a history of chronic bronchitis. The physical characteristics of the two groups of subjects were similar (table 1). Physical examination showed nothing abnormal in any of the subjects.

### SPIROMETRY

Vital capacity (VC) and forced expiratory volume in one second (FEV<sub>1</sub>) were measured with a spirometer based on a pneumotachograph (Vitalograph Compact, Vitalograph Ltd, Buckingham) as the best of three measurements. The results were related to predicted normal values.<sup>7</sup>

### PULMONARY CLEARANCE OF <sup>99m</sup>Tc DTPA

A solution of <sup>99m</sup>Tc DTPA was prepared from a commercially available kit (Pentetate II, Amersham International, Amersham) and nebulised with an air jet nebuliser (UltraVent, Mallinckrodt Diagnostica, Petten, The Netherlands). The mass median diameter of the particles was 1.7 μm. The subjects inhaled the aerosol by quiet tidal breathing for one to two minutes while seated in front of a gamma camera (Maxicamera 400T, General Electric Company, Milwaukee, Wisconsin) until a count rate of about 2000 counts/second had been reached. The subjects were then placed immediately in the supine position on a thin couch and the gamma camera was placed under the couch to obtain a posterior image of the lungs. The gamma camera was interfaced with a computer system and the measurements of radioactivity over the chest were stored in one minute frames for 180 minutes in a 64 × 64 image matrix. After about 170 minutes a small amount of <sup>99m</sup>Tc DTPA was injected intravenously to enable a correction for non-pulmonary radioactivity to be performed.

The measurements were analysed by selecting a region of interest that enclosed both

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Table 1 Characteristics and spirometric values of the subjects studied (mean (SD))

	Smokers (n = 9)	Non-smokers (n = 13)
Age (y)	48 (6)	43 (4)
Height (m)	1.80 (0.04)	1.78 (0.05)
Weight (kg)	75 (8)	73 (11)
Tobacco consumption (cigarettes/day)	17 (6)	
VC (% pred)	110 (10)	110 (9)
FEV <sub>1</sub> (% pred)	102 (16)	106 (12)

lungs and by generating a time-activity curve. The correction for non-pulmonary radioactivity was performed as described by Barrowcliffe *et al.*,<sup>8</sup> a background region being selected over the great vessels in the abdomen.

#### PULMONARY ABSORPTION OF TERBUTALINE

All subjects were studied at the same time in the morning after a fast of about 10 hours. The smokers were asked not to smoke before the measurements on the study day. To avoid buccal or gastrointestinal absorption of terbutaline, each subject was given a suspension of 5 g of charcoal in 25 ml of water to drink during the two minutes before and after the inhalation of terbutaline. In addition, subjects swallowed 10 g of charcoal dispensed in 50 ml of water one and two hours after the inhalation of terbutaline. They were instructed to swirl the charcoal suspension around in the mouth before swallowing it. The administration of charcoal has been shown to be effective in inhibiting the systemic absorption of terbutaline administered orally.<sup>9</sup>

The absorption of terbutaline from the airways was studied twice in each subject with two different modes of inhalation. The order of the modes of inhalation was randomised, and a washout period of one to four weeks was allowed to elapse between the two parts of the study. On one study day a solution of terbutaline sulphate (2.5 mg/ml) was nebulised with an UltraVent nebuliser and the subject inhaled the aerosol by quiet tidal breathing for three minutes. The duration of inhalation was chosen on the basis of preliminary experiments, so that the dose of terbutaline delivered to the lungs was similar to the dose in two inhalations of dry terbutaline sulphate powder (see below).

On the other study day the subject inhaled two doses (2 × 0.5 mg) of terbutaline sulphate from a powder inhaler (Turbuhaler, AB Draco, Lund, Sweden). Airflow during the inhalation was monitored with a pneumotachograph (Vitalograph Compact) arranged in series with the Turbuhaler and modified for measuring flow during inhalation; peak inspiratory flow was recorded.

Venous blood was sampled from a catheter inserted into a brachial vein before and three, five, eight, 10, 15, 20, 30, 45, 60, 120, and 240 minutes after the inhalation of terbutaline. The samples were centrifuged immediately and plasma was frozen at -18 °C for subsequent measurement of the concentration of terbutaline by gas chromatography and mass spectrometry.<sup>10</sup> After dry powder administra-

tion of terbutaline, urine was collected for 36 hours and the total excreted amount of terbutaline was calculated.

#### STATISTICAL ANALYSIS

Individual curves of plasma terbutaline concentration versus time were used to obtain the maximum plasma concentration (C<sub>max</sub>) and the time to maximum plasma concentration (t<sub>max</sub>). The rate of appearance of terbutaline in plasma (increase rate) was expressed as the slope of the straight line (best fit) through the origin, time points being used up to and including t<sub>max</sub>. Unless otherwise stated, results are presented as means (with standard deviations in parentheses) in the smokers and non-smokers. For the two modes of administration, the variables C<sub>max</sub>, t<sub>max</sub>, and rate of increase were analysed first by analysis of variance. We then calculated the mean value after each administration for each patient and compared the means between smokers and non-smokers, using a *t* test without the assumption of equal variances between the two groups. Corresponding 95% confidence limits were computed. The level of significance was set at *p* = 0.05.

#### Results

All subjects had normal spirometric values (table 1).

The inhaled <sup>99m</sup>TcDTPA showed a uniform distribution throughout the lungs in all subjects (fig 1). Composite curves for the mean values for clearance of <sup>99m</sup>Tc DTPA from the lungs in smokers and non-smokers are shown in figure 2. In the non-smokers the count rate over the lungs fell monoexponentially to 50% of the initial value after 71 minutes. The clearance curve from the smokers had a steep initial slope, so that 50% of the initial count rate was reached after 21 minutes.

Concentrations of terbutaline increased much faster in the smokers than in the non-smokers after inhalation of nebulised ter-

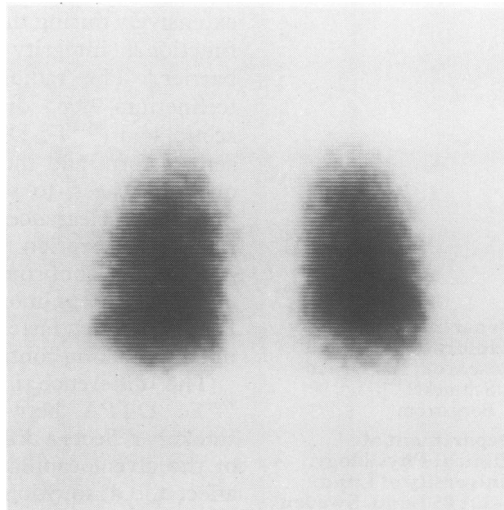


Figure 1 Gamma camera image obtained in the posterior view after inhalation of nebulised <sup>99m</sup>Tc labelled diethylenetriamine penta-acetic acid. The particles are distributed uniformly throughout the lungs.

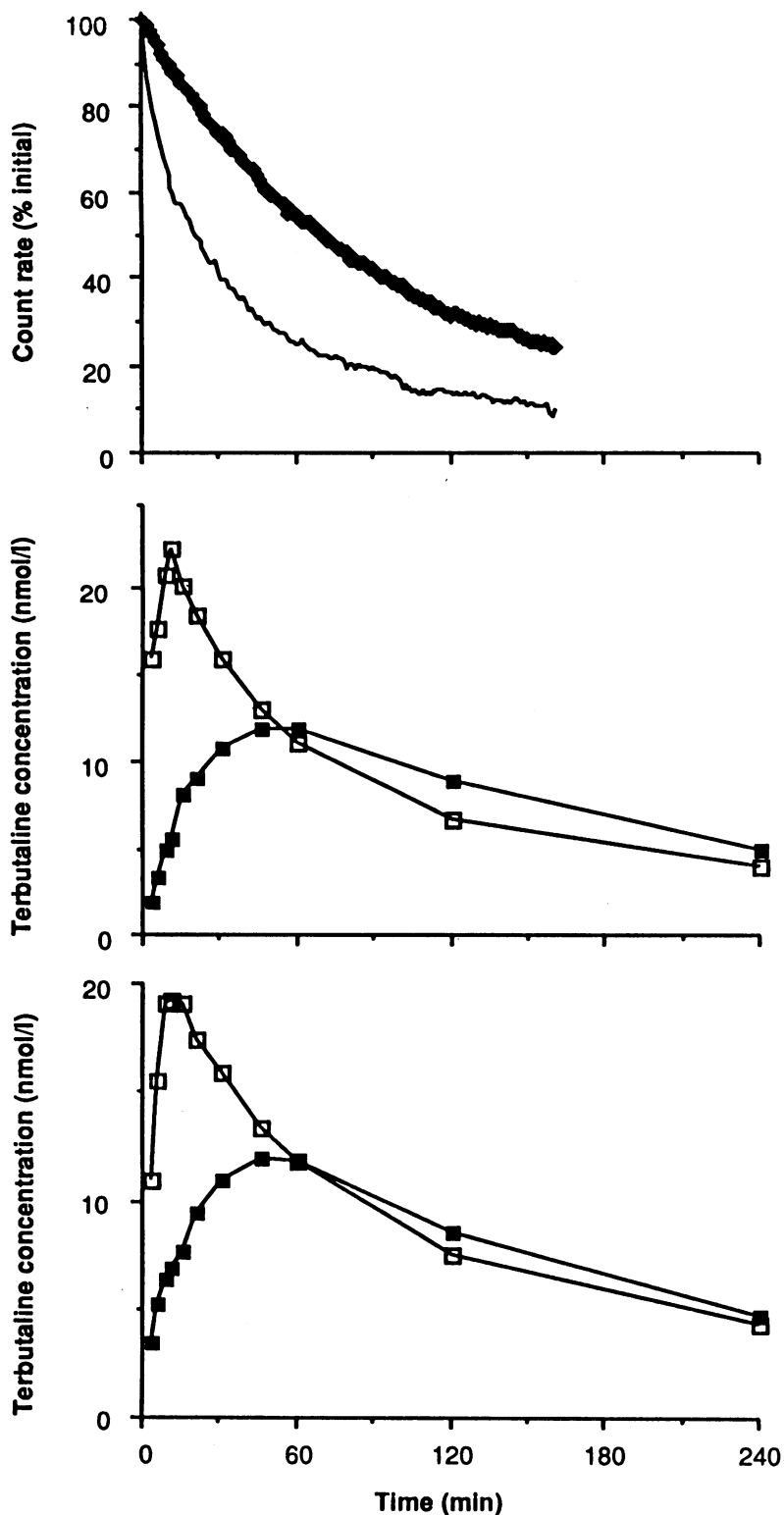


Figure 2 (a) Time-activity curves obtained over the lungs after inhalation of nebulised  $^{99m}\text{Tc}$  labelled diethylenetriamine penta-acetic acid (upper panel), 50% of the radioactivity being cleared from the lungs after 21 minutes in the smokers (thin line) and after 71 minutes in the non-smokers (thick line). (b) Plasma concentration of terbutaline after inhalation of terbutaline as a nebulised solution. (c) Plasma concentrations of terbutaline inhaled as a dry powder in smokers (open symbols) and non-smokers (closed symbols).

butaline or dry powder (fig 2). The  $C_{\text{max}}$  values were nearly twice as high in the smokers as in the non-smokers (table 2), the difference being 9.6 (confidence interval (CI) 0.6–18.7) nmol/l;  $p < 0.05$ . The  $t_{\text{max}}$  in the smokers was about one third of that in the non-smokers, the difference being 32 (CI 19–46) minutes;

$p < 0.0005$ . The rate of increase in terbutaline plasma concentration was much higher in the smokers than in the non-smokers. The difference was 2.1 (CI 0.8–3.3) nmol/l a minute;  $p = 0.005$ .

When the plasma terbutaline concentration curves were compared with respect to the mode of administration, very little difference was noted between inhalation of nebulised terbutaline and dry powder, either in smokers or in non-smokers (fig 1, table 2).

Mean peak inspiratory flow during inhalation of dry terbutaline powder was 59 (range 46–70) l/min in the smokers and 56 (range 44–70) l/min in the non-smokers. The mean (SD) total amount of terbutaline recovered in the urine after powder inhalation was 535 (131) nmol in the smokers and 563 (167) nmol in the non-smokers.

### Discussion

This study shows that the plasma concentration of terbutaline is substantially higher in smokers than in non-smokers during the first 30 minutes after its inhalation as a nebulised solution or as dry powder.

To ensure delivery of similar amounts of drug to all subjects, the inhalation procedure was standardised and monitored. We collected urine from the subjects after inhalation of dry terbutaline powder and found little difference in urinary excretion of terbutaline over 36 hours between smokers and non-smokers. This shows that the dose of drug delivered to the lungs was similar in the two groups of subjects.

Buccal and gastrointestinal absorption of terbutaline was inhibited by administering charcoal suspension to the subjects. Charcoal given in this manner has been shown to adsorb 97% of an oral dose of terbutaline.<sup>9</sup> The large differences in  $C_{\text{max}}$  and  $t_{\text{max}}$  after the inhalation indicate therefore that absorption of the inhaled drug from the lungs is much faster in smokers than in non-smokers. The smokers in this study were all free from respiratory symptoms and had normal spirometric values. The increased rate of terbutaline absorption is therefore most likely to be due to the effect of tobacco smoke on the physiological barrier functions in the lung.<sup>1</sup>

The differences in plasma concentration of terbutaline between smokers and non-smokers were seen with both modes of administration. Nebulised terbutaline when inhaled from an UltraVent nebuliser is deposited mainly in the peripheral airways (fig 1), whereas terbutaline inhaled as dry powder is deposited more in central airways.<sup>11</sup> Smoking therefore appears to affect the rate of terbutaline absorption from both central and peripheral airways.

The rationale for administering bronchodilators in aerosol form is to achieve a high local tissue concentration of the drug. The primary site of action of  $\beta_2$  agonists is the bronchial smooth muscle. The drug penetrates the airway mucosa to reach the smooth muscle by diffusion or via the microcirculation. If the penetration of the mucosa is faster in smokers than in non-smokers, this could result in a

Table 2 Mean (SD) maximum plasma concentration ( $C_{max}$ ), time to maximum plasma concentration ( $t_{max}$ ), and calculated rate of increase in plasma concentration after inhalation of nebulised terbutaline solution or dry powder in smokers and non-smokers, with 95% confidence limits for the differences between smokers and non-smokers

	Smokers (n = 9)		Non-smokers (n = 13)		Confidence interval
	Nebulised	Powder	Nebulised	Powder	
$C_{max}$ (nmol/l)	23 (16)	21 (9)	14 (4)	12 (4)	0.6–18.7
$t_{max}$ (min)	17 (17)	17 (17)	50 (10)	50 (7)	19–46
Rate of increase (nmol/l/min)	2.6 (2.2)	2.2 (1.4)	0.3 (0.1)	0.6 (0.6)	0.8–3.3

faster onset of the therapeutic action in smokers.

The peak plasma concentration of terbutaline was much higher in smokers than in non-smokers. The relation between bronchodilatation and plasma concentration after inhalation has been studied in asthmatic subjects by van den Berg,<sup>12</sup> who found that a clearly detectable airway effect was associated with a peak plasma concentration of about 2 nmol/l. The therapeutic range of terbutaline plasma concentration for systemic treatment is 10–25 nmol/l.<sup>13</sup> The mean peak plasma concentration found in the non-smokers in this study was below the lower limit of the therapeutic range for systemic treatment, indicating that little therapeutic effect may be expected from recirculating drug. The plasma concentrations in the smokers during the first hour after inhalation of terbutaline were higher, and recirculating drug could therefore contribute to bronchodilatation in smokers. Systemic side effects after inhalation of terbutaline may also be more common in smoking than in non-smoking subjects. Side effects were not assessed in this study.

The difference in the rate of increase in plasma concentration indicates that terbutaline is removed from the lungs at a higher rate in smokers than in non-smokers. To the extent that this reflects a difference in the rate of decline in terbutaline concentration at the site of action, it suggests that the duration of the therapeutic effect may be shorter in smoking than in non-smoking subjects. This could not be tested in this study of normal subjects.

The influence of lung disease on the pulmonary absorption of terbutaline is largely unknown, but some inference can be made from studies of the pulmonary clearance of <sup>99m</sup>TcDTPA. Most of the available evidence suggests that there is no great increase in the alveolocapillary transfer of <sup>99m</sup>TcDTPA in non-smokers with stable asthma.<sup>6,14,15</sup> Increased lung volume<sup>16,17</sup> and ventilation with a large tidal volume,<sup>18</sup> as occurs during exercise,<sup>19</sup> augment the pulmonary clearance of <sup>99m</sup>TcDTPA. This may be relevant to bronchodilator aerosol treatment of patients with asthma with hyperinflation or exercise induced asthma. Increased pulmonary clearance of <sup>99m</sup>TcDTPA has been reported in many interstitial lung diseases, such as sarcoidosis.<sup>20</sup> Air-flow obstruction is common in sarcoidosis,<sup>21</sup> and patients treated with inhaled terbutaline

may have a faster pulmonary absorption of the drug than normal subjects.

We have shown that the pulmonary absorption of terbutaline is much faster in smokers than in non-smokers. This may be relevant to its therapeutic effect, by giving a faster onset of action and a shorter duration of the therapeutic effect in smokers than in non-smokers. Further studies of the relation between smoking habits and the efficacy of aerosol bronchodilator treatment are warranted.

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- Barrowcliffe MP, Jones JG. Solute permeability of the alveolar capillary barrier. *Thorax* 1987;42:1–10.
- Jones JG, Lawler P, Crawley JCW, Minty BD, Hulands G, Veall N. Increased alveolar epithelial permeability in cigarette smokers. *Lancet* 1980;i:66–8.
- Dusser DJ, Minty BD, Collignon MAG, Hinge D, Barritault LG, Huchon GJ. Regional respiratory clearance of aerosolized <sup>99m</sup>Tc-DTPA: posture and smoking effects. *J Appl Physiol* 1986;60:2000–6.
- Huchon GJ, Russel JA, Barritault LG, Lipavsky A, Murray JF. Chronic air-flow limitation does not increase respiratory epithelial permeability assessed by aerosolized solute, but smoking does. *Am Rev Respir Dis* 1984;130:457–60.
- Kennedy SM, Elwood RK, Wiggs BJR, Paré PD, Hogg JC. Increased airway mucosal permeability in smokers. *Am Rev Respir Dis* 1984;129:143–8.
- O'Byrne PM, Dolovich M, Dirks R, Roberts RS, Newhouse MT. Lung epithelial permeability: relation to nonspecific airway responsiveness. *J Appl Physiol* 1984;57:77–84.
- Quanjer PHH, ed. Standardized lung function testing. *Bull Eur Physiopathol Respir* 1983;19:(suppl 5).
- Barrowcliffe MP, Otto C, Jones JG. Pulmonary clearance of <sup>99m</sup>Tc-DTPA: influence of background activity. *J Appl Physiol* 1988;64:1045–9.
- Borgström L, Nilsson M. A method for determination of the absolute pulmonary bioavailability of inhaled drugs: terbutaline. *Pharmaceut Res* 1990;7:1068–70.
- Borgström L, Nyberg L, Jönsson S, Lindberg C, Paulson J. Pharmacokinetic evaluation in man of terbutaline given as separate enantiomers and as the racemate. *Br J Clin Pharmacol* 1989;27:49–56.
- Newman SP, Morén F, Trofast E, Woodman G, Clarke SW. Deposition patterns in man from Turbuhaler: a preliminary report. In: Newman SP, Morén F, Crompton GK, eds. *A new concept in inhalation therapy*. Bussum: Medicom, 1987:104–14.
- van den Berg W. *Pharmacodynamics of terbutaline*. Thesis, University of Utrecht, 1982:71–7.
- Lefterink JG. *Terbutaline, analytical, clinical pharmacological and toxicological aspects*. Thesis, University of Utrecht, 1979:101–15.
- Elwood RK, Kennedy S, Beltzberg A, Hogg JC, Paré PD. Respiratory mucosal permeability in asthma. *Am Rev Respir Dis* 1983;128:523–7.
- Rees PJ, Shelton D, Chan TB, Eiser N, Clark TJH, Maisey MN. Effects of histamine on lung permeability in normal and asthmatic subjects. *Thorax* 1985;40:603–6.
- Marks JD, Luce JM, Lazar NM, Wu JNS, Lipavsky A, Murray JF. Effect of increases in lung volume on clearance of aerosolized solute from human lungs. *J Appl Physiol* 1985;59:1242–8.
- Nolop KB, Maxwell DL, Royston D, Hughes JMB. Effect of raised thoracic pressure and volume on <sup>99m</sup>Tc-DTPA clearance in human lungs. *J Appl Physiol* 1986;60:1493–7.
- Evander E, Wollmer P, Jonson B. Pulmonary clearance of inhaled <sup>99m</sup>Tc-DTPA: effects of ventilation pattern. *Clin Physiol* 1990;10:189–99.
- Meignan M, Rosso J, Leveau J, et al. Exercise increases the lung clearance of inhaled technetium-99m DTPA. *J Nucl Med* 1986;27:274–80.
- Dusser DJ, Collignon MA, Stanislas-Leguern G, Barritault LG, Chrétien J, Huchon GJ. Respiratory clearance of <sup>99m</sup>Tc-DTPA and pulmonary involvement in sarcoidosis. *Am Rev Respir Dis* 1986;134:493–7.
- Brådvik I, Wollmer P, Simonsson B, Albrechtsson U, Lyttkens K, Jonson B. Lung mechanics and their relationship to lung volumes in pulmonary sarcoidosis. *Eur Respir J* 1989;2:643–51.