Penetration of minocycline into lung tissues

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The penetration of minocycline into different lung tissues and bronchial mucus was studied in 17 patients undergoing pulmonary surgery for cancer. The patients received oral minocycline 100 mg at night for 3 days preceding surgery. Minocycline concentrations were measured in plasma samples collected before the operation and in tissues and mucus taken from in and around the part of the lung that was surgically removed. Mean tissue or mucus concentration to plasma concentration ratios were 3.78 ± 1.10 for lung parenchyma, 4.04 ± 1.31 for bronchial walls, 3.37 ± 1.00 for pulmonary arterial walls, 1.99 ± 1.80 for intraluminal mucus collected from bronchi located in healthy tissue proximal to the tumour, 5.16 ± 3.26 for intraluminal mucus collected in a bronchus distal to the tumour, and 3.06 ± 1.99 for catheter-collected mucus from the trachea and principal bronchi. These results indicate that minocycline is found in high concentration in all types of lung tissue and mucus in man.

Keywords lung minocycline tissue penetration

Introduction

Minocycline is a second generation tetracycline characterized by a prolonged elimination half-life (13 to 18 h) and a high affinity for lipids, as shown by a high partition coefficient, which ensures good tissue penetration (Saivin & Houin, 1988).

The penetration of minocycline into the lower respiratory tract has hitherto been evaluated by measuring concentrations of this antibiotic in bronchial secretions obtained by expectoration (sputum) (Brogan *et al.*, 1977; Clauzel *et al.*, 1978; Maesen *et al.*, 1989). However, global concentrations in lung tissue were measured by McDonald *et al.* (1973) in three patients and by Naline *et al.* (1991) in 14 patients. These two studies showed, that unlike the concentrations obtained in bronchial secretions, minocycline concentrations in lung tissue were high, with a mean lung tissue/plasma drug concentration ratio of 3.17 ± 1.53 , as compared with a sputum/plasma drug concentration ratio varying between 0.3 and 2.8 (Brogan *et al.*, 1977; Clauzel *et al.*, 1978; Maesen *et al.*, 1989).

In the present study we evaluated the penetration of minocycline into different types of human 'lung tissue', namely into the walls of bronchi and pulmonary arteries, as well as into lung parenchyma proper, and into mucus collected at different levels of the broncho-tracheal tree. Since the patients who entered the study were undergoing surgery for lung cancer, the penetration of minocycline into tumour tissue and into mucus from the

terminal bronchi distal to the tumoural obstruction was also evaluated.

Methods

Seventeen male patients aged from 38 to 89 years (mean: 60 ± 15 years) who were about to undergo thoracic surgery participated in this study. Thoracotomy and pulmonary excision were being performed for lung cancer. The diagnosis was squamous carcinoma in 10 cases, adenocarcinoma in 6 cases and undifferentiated carcinoma in 1 case. The experimental procedure complied with the Helsinki declaration and was approved by the Ethics Committee of the Centre Hospitalier de Versailles. All patients had given their written informed consent to the study.

During the 3 days preceding the surgical operation, each patient swallowed a 100 mg capsule of minocycline (Mynocine[®], Lederle) at night. The surgical operation began 13 to 20 h after dosing. Venous blood was withdrawn and collected on lithium heparinate just before the surgical procedure started. During surgery, fragments of lung parenchyma, bronchi, pulmonary artery and tumour were removed from the part of the lung that was excised. In addition, bronchial mucus was collected from the trachea and principal bronchi by catheteriz-

Table 1 Concentrations of minocycline in plasma, erythrocytes, intrabronchial mucus collected at various levels and in various lung tissues. Values are mean $\pm$ s.d.

Tissue	n	Plasma concentration ($\mu\text{g ml}^{-1}$)	Tissue concentration ($\mu\text{g g}^{-1}$)	Tissue/plasma ratio	Correlation (r)
Erythrocytes	9	0.61 $\pm$ 0.20	0.55 $\pm$ 0.14	0.94 $\pm$ 0.29	0.659
Catheter-collected mucus from principal bronchi	5	0.63 $\pm$ 0.27	1.67 $\pm$ 1.11	3.06 $\pm$ 1.99	0.1
Intrabronchial mucus proximal to tumour	13	0.82 $\pm$ 0.46	1.45 $\pm$ 1.08	1.99 $\pm$ 1.80	0.595 ‡
Intrabronchial mucus distal to tumour	10	0.80 $\pm$ 0.37	4.51 $\pm$ 3.15	5.16 $\pm$ 3.26	0.713 ‡
Healthy lung parenchyma	15	0.83 $\pm$ 0.43	3.02 $\pm$ 1.44	3.78 $\pm$ 1.10	0.84 †
Tumoral tissue	11	0.79 $\pm$ 0.47	2.46 $\pm$ 1.30	3.16 $\pm$ 0.72	0.942 †
Bronchial wall	11	0.79 $\pm$ 0.46	2.99 $\pm$ 1.26	4.40 $\pm$ 1.31	0.805 †
Arterial wall	10	0.75 $\pm$ 0.46	2.6 $\pm$ 1.87	3.37 $\pm$ 1.00	0.951 †

Significant correlations between plasma and tissue drug concentrations are shown as ‡ $P < 0.05$, † $P < 0.001$.

n = number of observations. r is the correlation between plasma and tissue drug concentration.

ation, and directly from segmental bronchi in healthy areas proximal and distal to the tumour. All of the samples were taken immediately to the laboratory where they were either centrifuged (plasma) or carefully dried on blotting paper (tissue fragments) and stored at -80°C pending minocycline assay.

Minocycline was assayed in blood and tissues according to the h.p.l.c. method described by Naline *et al.* (1991). The limit of assay was $0.1 \mu\text{g ml}^{-1}$. Within- and between-day coefficients of variations were $< 10\%$ for the concentration range 0.2 to $10 \mu\text{g ml}^{-1}$.

The values reported in the text are expressed as mean $\pm$ s.d. Statistical analysis of the results was performed using Student's t -test for unpaired data.

Results

The concentrations of minocycline measured in plasma, erythrocytes, broncho-pulmonary fragments and mucus are shown in Table 1. Concentrations of minocycline were similar in plasma and erythrocytes but higher in the other tissues. There were no significant differences in mean concentrations between the different pulmonary fragments and mucus.

The pulmonary tissue/plasma concentration ratios for healthy lung parenchyma, bronchi and pulmonary arterial walls were not significantly different. Similarly, there was no significant difference in mucus/plasma drug concentration ratios between catheter-collected mucus from the trachea and principal bronchi and mucus collected from segmental bronchi distal to the tumoral obstruction or the tissue/plasma drug concentration ratios. However, the mucus/plasma drug concentration ratio for the mucus collected proximal to the tumour (1.99 ± 1.80 ; $P < 0.05$) was significantly lower than the ratios obtained for the pulmonary arterial wall, the lung tissue proper and the wall of the principal bronchi.

The data in Table 1 indicate a significant correlation between minocycline concentrations in plasma and in

healthy lung parenchyma, bronchi, tumoral tissue and arterial wall ($P < 0.001$), and in mucus collected from bronchi distal and proximal to the tumour ($P < 0.05$). Conversely, there was no significant correlation between minocycline concentrations in plasma and in catheter-collected mucus from the trachea and principal bronchi, or in erythrocytes.

Discussion

The penetration of antibiotics into the lower respiratory tract can be evaluated by measuring concentrations in the bronchial secretions and/or the so-called 'lung tissue'. Since bronchial secretions can easily be collected as expectorated mucus (sputum), the first method is the most widely used, but it is open to criticism. Thus, the mucus secreted by the bronchi may be diluted with saliva, and the therapeutic effectiveness of the amount of antibiotic it contains is doubtful. Measurements of antibiotic concentrations in bronchial secretions are sometimes considered useful only in acute exacerbations of chronic bronchitis, in bacterial superinfection of viral lung diseases, or in mycoplasma infections where only the surface of the bronchial mucosa is involved due to the micro-organism being attached to this surface (Dureux *et al.*, 1982; Lambert, 1978; Lode *et al.*, 1980). Finally, at all doses there are wide interindividual variations in antibiotic concentration in mucus owing to differences in the volume of bronchial mucus secreted, in the degree of pulmonary and bronchial inflammation and in the rate of mucociliary clearance (Dureux *et al.*, 1982). Measurement of antibiotic concentrations in lung tissues represents a more rational approach to establishing therapeutic levels, although the assays are usually performed on healthy tissue and the values obtained do not necessarily reflect the situation in infected areas (Dureux *et al.*, 1982).

The bronchial secretion (sputum)/plasma concentration ratios of minocycline reported in the literature

vary between 0.3 and 0.9 (Brogan *et al.*, 1977; Maesen *et al.*, 1989) or between 0.83 and 2.18 (Clauzel *et al.*, 1978). Our results show that when bronchial mucus is collected *in situ* the amount of antibiotic it contains is much higher: the mean mucus/plasma drug concentration ratios found in our study were 3.06 ± 1.99 for mucus collected by catheterization from the principal and segmental bronchi ($n = 5$), 1.99 ± 1.80 for mucus collected from segmental and alveolar bronchi proximal to the tumoral obstruction ($n = 13$), and 5.16 ± 3.26 for mucus collected from bronchi distal to the obstruction ($n = 10$). These data indicate the limitations of results obtained

when minocycline (and probably other antibiotics) are assayed in sputum collections. Our results also show that minocycline is present in high concentrations in all lung tissues. In our 17 patients, the mean lung tissue/plasma concentration ratio varied from 3.37 ± 1.00 for arterial wall to 4.04 ± 1.31 for bronchial wall. These values are similar to those reported by McDonald *et al.* (1973) in three patients (3.13 to 4.47) and by Naline *et al.* (1991) in 14 patients (mean: 3.17 ± 1.53). Moreover, we found that minocycline was present in similar concentrations in malignant tumours.

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