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SHORT COMMUNICATION

RELATIONSHIP BETWEEN LUNG TISSUE AND BLOOD PLASMA CONCENTRATIONS OF INHALED BUDESONIDE

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ABSTRACT

In 11 patients, in whom a lung lobe or whole lung was to be resected, a single dose of 1·6 mg inhaled budesonide was given pre-operatively. In 9 of them, concentrations of the drug in both lung tissue and blood plasma were measured. Budesonide concentrations in lung tissue, at least 90 min after dosage, were 2·1–8·9 nmol kg^{-1}. Concentrations in blood plasma (0·27–1·1 nmol kg^{-1}) were 1/8th of those in lung tissue.

KEY WORDS Lung Plasma Budesonide Glucocorticosteroid

INTRODUCTION

Inhaled glucocorticosteroids have been used with success in chronic asthma and other obstructive lung diseases.[1,2] Also in interstitial lung diseases like sarcoidosis, high doses of an inhaled steroid might be effective.[3,4]

In the present pilot study, performed in lung cancer patients, undergoing thoracotomy, budesonide was administered by inhalation prior to surgery. The concentration of the drug was measured in blood plasma and lung parenchyma samples. This kinetic approach, applied for the first time with an inhalation steroid, may be valuable for clarifying concentration–effect relationships after local drug administration.

METHODOLOGY

Protocol

The study was approved by the local hospital's medical ethics committee. Informed consent was obtained in 11 patients (10 males) with bronchial carcinoma, who were referred for thoracotomy. Their mean age was 68 years

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(range 44–83); 10 patients had squamous cell carcinoma, and 1 had an adenocarcinoma. Their vital capacity was 2·9–4·8 (80–123 per cent of predicted), their forced expiratory volume in one second (FEV_1) was 1·6–3·3 (57–115 per cent of predicted).

On the morning of the thoracotomy, 1·60 mg budesonide (equal to 3·7 μmol) was administered via a large volume spacer, Nebuhaler® (eight puffs each of 0·20 mg). The time of administration was recorded. During general anaesthesia, thoracotomy was performed and resection of a lung lobe or whole lung followed in 10 patients. At least 90 min passed between inhalation and resection. A part of the obtained material, macroscopically free of tumour and visible bronchi, was prepared to obtain 'lung parenchyma' for analysis of budesonide. During the operation, a blood sample was drawn to obtain blood plasma for analysis.

Quantitation of budesonide in plasma

The assay of budesonide was based on the use of a radioimmunoassay (RIA) after isolation of the separate epimers by high performance liquid chromatography (HPLC).[5] Before HPLC, budesonide was extracted from the blood plasma samples on to C_{18} column cartridges, which thereafter were washed with water and 40 per cent methanol before budesonide was eluted with ethanol. Citrate was added to the eluate and the ethanol was evaporated. The residue was redissolved in 275 μl mobile phase and 200 μl was injected into the HPLC-system, equipped with a guard column (~37–50 μm Corasil C_{18}) and an analytical column (5 μm Spherisorb ODS 5·0×240 mm), thermostated at 23·0 °C. As mobile phase consisting of ethanol and 3·5 mM citrate (~43: 57) was used, giving a resolution of ~1·5 between the epimers of budesonide. The epimer fractions were collected by time, evaporated and redissolved in phosphate buffer before RIA. Each epimer was separately quantified in a RIA based on the use of an antiserum raised against budesonide coupled to ovalbumin, with tritium-labelled budesonide as the marker and dextran-coated charcoal as the separating agent.[6] Analytical performance study showed the intra- and inter-assay coefficients of variation to be in the range 1·7–3·8 per cent and 4·0–8·2 per cent, respectively, when budesonide added to 3·0 ml of blood plasma (0·23–3·5 nmol l^{-1}) was analysed. Accuracy was in the range of 97·2–111 per cent. The lower limit of quantitation for each epimer was 0·23 nmol l^{-1} (0·1 ng ml^{-1}).[5] The density of blood plasma was assumed to be 1·0 kg l^{-1}.

Quantitation of budesonide in lung tissue

The assay was basically the same as for quantitation of budesonide in blood plasma, but the pretreatment of the sample before HPLC differed. Lung tissue was homogenized in buffer and digested with a proteolytic enzyme (subtilisin) at pH 8·0, 50 °C for 2 h. The digest was extracted with methylene chloride, evaporated and redissolved in 2·0 ml mobile phase, then 200 μl was injected

into the HPLC-system. A limited performance study showed the intra-assay coefficient of variation to be in the range of 2·5–3·0 per cent when budesonide added to 4·0 g lung tissue (23·2–46·4 nmol kg^{-1}) was analysed. Accuracy was in the range 81·2–99·9 per cent. The lower limit of quantitation for each epimer was 0·80 nmol kg^{-1} (0·35 ng g^{-1}).

RESULTS

In one patient, no resection was carried out and in one patient, the obtained sample was too small to be processed. The budesonide concentrations obtained in lung tissue and in blood plasma from the remaining nine patients are given in Table 1. In Figure 1, the data are plotted versus time after drug administration.

The mean budesonide concentration in lung tissue, compared with the mean concentration in blood plasma, was 8·7 times higher. Owing to technical reasons, there was a time difference (range −90 to +60 min) between sampling of lung specimens and sampling of plasma. However, regression analysis of the two sets of data in Figure 1 shows that lung and plasma levels fall almost in parallel. At 150 min (the mean sampling time) the two lines differed by a factor of 7·9.

DISCUSSION

After inhalation of aerosolized budesonide via a spacer, the dose reaching the subject is deposited in the lungs to a major extent. Budesonide is then rapidly absorbed into the systemic circulation without any presystemic metabolism. Oral

Table 1. Budesonide concentrations in lung tissue and in blood plasma following administration of 1·60 mg (3·7 μmol) inhaled budesonide

Patient number	Sex	Age (yr)	Body weight (kg)	FEV_1 (l)	Lung tissue		Blood plasma	
					Time* (min)	Conc. (nmol kg^{-1})	Time* (min)	Conc. (nmol kg^{-1})
1	M	61	80	2·4	90	6·0	60	1·11
2	M	70	79	3·3	150	3·4	90	0·77
4	M	69	76	2·1	120	(2·1)†	135	(0·28)†
6	M	51	74	2·0	180	8·9	180	0·74
7	M	83	70	1·8	90	8·2	105	0·92
8	M	82	71	1·9	105	3·7	135	(0·27)†
9	M	68	60	2·5	135	7·4	225	0·55
10	M	63	72	1·6	180	3·9	210	0·64
11	M	76	73	2·0	240	2·8	225	(0·40)†
Mean		69	73	2·2	143	5·5	155	0·63

*Time interval between budesonide administration and sampling.
†Values within parentheses are estimates, because they are at the lower limit of quantitation.

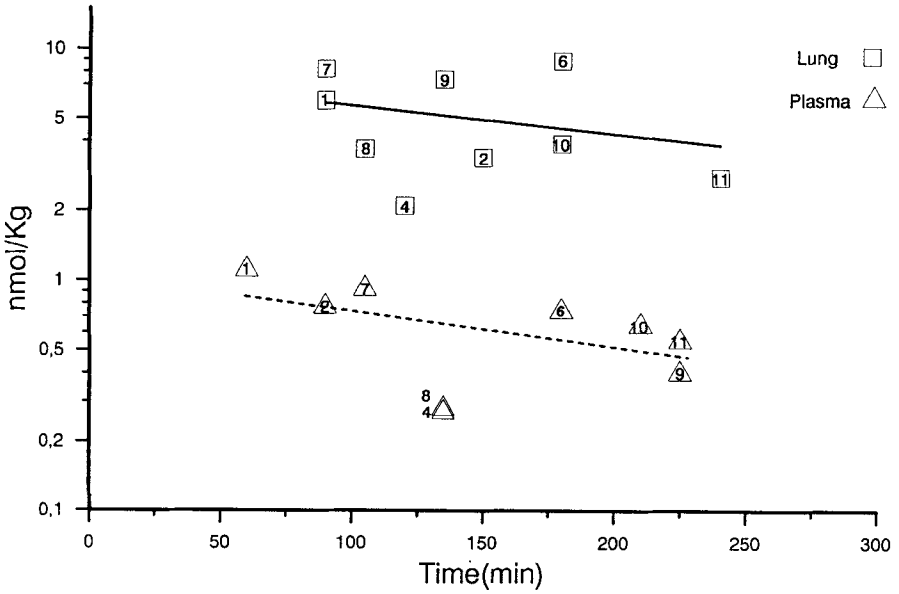

Figure 1. Budesonide concentrations in human lung tissue (□) and in blood plasma (△) after inhalation of 1·60 mg (3·7 μmol) budesonide. Figures in each symbol denote subject number. The straight lines were obtained by regression analysis of the two sets of data. The slope was 0·0027 min^{-1} for the lung data and 0·0026 min^{-1} for the blood plasma data

budesonide, however, is metabolically labile and is inactivated to about 90 per cent during first pass through the liver.[7]

In the present study, the samples were taken at a time-point where the lung absorption should have been complete. From our data, on the assumption of 90 per cent plasma protein binding,[7] the lung tissue/unbound blood plasma distribution ratio for budesonide can be estimated to be 87 (range 44–137). The lung tissue/unbound blood plasma distribution ratio for prednisolone during constant intravenous infusion in the rabbit is about 3.[8] The anti-asthma potency of inhaled budesonide has been estimated to be 33 times that of oral prednisolone.[9] This difference in glucocorticoid potency may be related to the relatively high lung concentrations achieved when inhaling budesonide.

Concentration data at appropriate local tissue sides, similar to those presented in this pilot study, may be an aid in predicting the therapeutic outcome of different formulations and routes of administration.

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