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運 書

THE INFLUENCE OF SEAPROSE ON ERYTHROMYCIN PENETRATION INTO BRONCHIAL MUCUS IN BRONCHOPULMONARY INFECTIONS

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Summary: In bronchopulmonary infections antibiotics can be combined with other drugs, called mucoactive drugs, that act to reduce the abnormal viscoelasticity of the mucus enabling a deeper penetration of more antibiotic into the mucus. Seaprose is a protease that interacts with the polymeric fibrillar structure of the bronchial mucus to shorten the long chains of mucoproteins, DNA and other macromolecules, thus reducing the viscosity of the mucus. In order to assess whether the combination of seaprose (60 mg/8 h) plus erythromycin (500 mg/8 h) allows higher antibiotic levels in sputum than erythromycin (500 mg/8 h) plus placebo, the pharmacokinetic behaviour in sputum and in blood of these two treatments was investigated in a double-blind study in two groups of twenty patients each with bronchopulmonary infections. Serum and sputum levels were determined for each patient at the first and seventh day of the two drug regimens. Statistically significant differences for peak, AUC and MRT, were observed for erythromycin between the first and last dose in the group of patients treated with seaprose plus erythromycin; moreover significant differences for these parameters were observed between the two groups. These findings indicate the presence of a pharmacokinetic synergism between seaprose and erythromycin which allows erythromycin to penetrate bronchial secretion more easily and in higher amounts, performing a sterilizing action with therapeutic advantages

Introduction

A common finding in bronchopulmonary infections is thickening of bronchial mucus, with consequent different degrees of impairment of mucociliary clearance. The presence of a thick purulent bronchial mucus containing a large amount of pathogenic bacteria requires not only that the chosen antibiotic reaches high levels in blood or lungs, but also that it can penetrate inside the mucus at high

enough concentrations for long enough durations to have sterilizing effects (1). Thus proper antibacterial therapy is based on the premise that the antibiotic is chosen because it is active against the specific pathogen and remains in active but nontoxic concentrations at the site of infection long enough to exert its antimicrobial activity (2)

These considerations are particularly true for therapy of respiratory infections. In fact, several authors (3-11) investigating the causes of failure to cure in respiratory infections found that, along with other factors, the common denominator in the

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and the gum at the mandibular and maxillary levels and under the tongue at the outlets of the parotid, submaxillary, and sublingual salivary glands (a total of five rolls were used), then the patient coughed and sputum was collected. As published (18, 19), mucus collected by this non-invasive technique is ideally free of salivary contamination and the technique is simple, routinely applicable, easy, and well tolerated by the patient. Sampling by bronchofibroscopy or other invasive techniques was not performed for ethical reasons, since the clinical situation of the patients did not require such operations.

Mucus samples were collected at 1, 2, 3, 4, 6, 8 h following drug administration. Because not all patients were able to release sufficient amounts of mucus within a 1-h interval, the patients were divided into two subgroups, the first released mucus after 1, 3, 6 h while the other released mucus after 2, 4, 8 h. All samples were stored at -20°C until analysed.

Each patient urinated immediately before drug intake and all urine passed thereafter was collected at 2-h intervals over a period of 8 h. The volume of each specimen of urine was recorded and two 10 ml aliquots were taken each time. Blood, sputum and urine samples were collected by the same procedures after the last administration, urine up to the 12th hour.

Serum, sputum (after homogenization) and urine levels of erythromycin were assayed by the method of Grove and Randall (20), modified by Chabbert and Boulingre (21) by diffusion in agar medium, using *Sarcina lutea* ATCC 9341 as the test organism. All samples were assayed in triplicate. This method is sensitive to a concentration of 0.1 $\mu\text{g/ml}$ of erythromycin. Pharmacokinetic evaluation was based on the serum level data for each patient according to a first-order one-compartment open model, using a curve-fitting computer programme. For each subject the following parameters were estimated: K_a , K_e , C_{p0} , half-life, apparent volume of distribution, AUC, total clearance, AUMC and MRT.

The serum half-life was calculated from the equation:

$$t_{1/2} = \frac{\ln 2}{K_e}$$

in which $\ln 2$ is natural logarithm of 2 and K_e is the elimination constant. The area under the serum concentration/time curve (AUC) was calculated by computer, using the trapezoidal rule, and the estimation of the remaining area from the last sampling time to infinity was calculated by

$$\text{AUC}^{12-\infty} = \frac{C_x}{K_e}$$

The total clearance, which characterizes the clearing of the hypothetical plasma volume of a drug, was determined using the following equation:

$$Cl_{\text{tot}} = \frac{\text{Dose}}{\text{AUC}_{\infty}^0}$$

For each patient, the sputum concentrations of erythromycin were analysed by a curve-fitting computer programme, as described previously for serum data. The AUC values in this case give information about the bioavailability of erythromycin in sputum. A specific penetrability index (2) was also calculated, such as the "partition ratio", e.g. the percentage ratios between the AUC for the mucus and the AUC for the blood:

$$\frac{\text{AUC}_{\text{SP}}}{\text{AUC}_{\text{S}}} \times 100$$

where SP is sputum and S is serum

Statistical analyses on the values of the parameters were carried out using the student's t-test (paired and unpaired data); differences of $p \leq 0.05$ were considered as significant

Results

The semilogarithmic plot of the mean serum levels

Table 1 Serum and sputum pharmacokinetic data after oral administration of erythromycin alone and erythromycin + seaprose

Parameters	Serum						Sputum					
	Erythromycin			Seaprose + erythromycin			Erythromycin			Seaprose + erythromycin		
	1st day	7th day	1st day	7th day	1st day	7th day	1st day	7th day	1st day	7th day	1st day	7th day
Peak (µg/ml)	1.04 ± 0.1	1.34* ± 0.18	1.22* ± 0.25	1.68* ± 0.19	0.95 ± 0.06	1.08 ± 0.1	1.2* ± 0.15	1.46** ± 0.21	0.95 ± 0.06	1.08 ± 0.1	1.2* ± 0.15	1.46** ± 0.21
Time to peak (h)	1	1	1	1	2.3 ± 0.57	2.3 ± 0.57	2	2.30 ± 0.57	2.3 ± 0.57	2.3 ± 0.57	2	2.30 ± 0.57
C ₀₋₆ (µg/ml)	1.50 ± 0.12	1.80 ± 0.34	1.74 ± 0.47	2.07 ± 0.2	2.06 ± 0.6	2.20 ± 0.9	1.93 ± 0.48	2.15 ± 0.29	2.06 ± 0.6	2.20 ± 0.9	1.93 ± 0.48	2.15 ± 0.29
K _e (h ⁻¹)	2.76 ± 0.57	0.89** ± 0.76	3.06 ± 1.0	1.67** ± 0.44	1.02 ± 0.19	1.49 ± 0.97	1.82 ± 0.88	1.39 ± 0.14	1.02 ± 0.19	1.49 ± 0.97	1.82 ± 0.88	1.39 ± 0.14
K _a (h)	0.32 ± 0.04	0.25 ± 0.1	0.27 ± 0.04	0.22 ± 0.1	0.31 ± 0.12	0.27 ± 0.09	0.21 ± 0.06	0.18 ± 0.02	0.31 ± 0.12	0.27 ± 0.09	0.21 ± 0.06	0.18 ± 0.02
t _{1/2} (h)	2.18 ± 0.17	3.11 ± 1.33	2.54 ± 0.35	3.20 ± 0.14	2.45 ± 1.04	2.68 ± 0.90	3.50 ± 1.06	3.90* ± 0.52	2.45 ± 1.04	2.68 ± 0.90	3.50 ± 1.06	3.90* ± 0.52
AUC [(µg/ml) h]	4.38 ± 0.75	6.74* ± 1.30	5.77 ± 1.9	8.64*** ± 0.47	5.04 ± 1.08	6.07 ± 0.91	7.00* ± 1.17	11.21*** ± 2.32	5.04 ± 1.08	6.07 ± 0.91	7.00* ± 1.17	11.21*** ± 2.32
AVD (l)	36.00 ± 3.26	30.84 ± 5.11	33.58 ± 7.22	25.51 ± 2.01	33.58 ± 7.22	25.51 ± 2.01	33.58 ± 7.22	25.51 ± 2.01	33.58 ± 7.22	25.51 ± 2.01	33.58 ± 7.22	25.51 ± 2.01
Cl _{CR} (ml/min)	193.90 ± 31.88	122.83 ± 31.17	157.42 ± 54.11	92.12 ± 6.15	193.90 ± 31.88	122.83 ± 31.17	157.42 ± 54.11	92.12 ± 6.15	193.90 ± 31.88	122.83 ± 31.17	157.42 ± 54.11	92.12 ± 6.15
AUMC [(µg/ml) h]	15.57 ± 3.61	35.54** ± 22.15	24.44 ± 10.61	44.25** ± 36.32	25.08 ± 12.48	30.50 ± 10.28	47.65 ± 18	71.57*** ± 24.73	25.08 ± 12.48	30.50 ± 10.28	47.65 ± 18	71.57*** ± 24.73
MRT (h)	3.53 ± 0.22	4.71 ± 17.68	4.16 ± 0.47	4.87 ± 0.21	4.00 ± 1.34	4.09 ± 0.95	5.81 ± 1.41	6.60* ± 0.58	4.00 ± 1.34	4.09 ± 0.95	5.81 ± 1.41	6.60* ± 0.58

* p ≤ 0.05 between the first and last dose.
 ** p ≤ 0.01 between the first and last dose.
 *** p ≤ 0.001 between the two regimens

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