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Plasma and sputum erythromycin concentrations in chronic bronchitis

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ABSTRACT Plasma and sputum concentrations of erythromycin were measured in 10 patients with chronic bronchitis during an eight-day course of a new formulation of erythromycin stearate. The plasma erythromycin levels compared favourably with the minimal inhibitory concentrations for common respiratory pathogens and indicated adequate gastrointestinal absorption when the drug was taken immediately before food. Sputum erythromycin levels were variable and in some patients low or undetectable. Measurable sputum erythromycin levels were approximately 10% of plasma levels with no evidence of accumulation and were of similar order of magnitude to the minimal inhibitory concentrations for common respiratory pathogens except *Haemophilus influenzae*. There was no correlation between sputum and plasma erythromycin levels. There was a trend for higher erythromycin levels in sputum containing increasing amounts of pus and also when plasma levels increased.

Erythromycin is an effective antibiotic for the treatment of streptococcal and staphylococcal upper respiratory tract infections.[1-3] *Mycoplasma pneumoniae* is also sensitive to erythromycin in vitro and this antibiotic has been shown to improve symptoms and shorten the clinical course of mycoplasmal respiratory infections.[1 4 5] Erythromycin, however, has not been used widely for the treatment of acute, infective exacerbations of chronic bronchitis. The most common infecting organisms are *Haemophilus influenzae* and *Streptococcus pneumoniae*, but some strains of *Haemophilus* species possess variable and reduced susceptibility to erythromycin compared with the pneumococcus.[6 7] Recently, Willey *et al*[8] have demonstrated ampicillin and erythromycin to be equally effective in the treatment of infective exacerbations of chronic bronchitis.

The purpose of this work was to study the penetration of erythromycin into bronchial secretions by comparing plasma and sputum erythromycin concentrations during an eight-day course of a new formulation of erythromycin stearate[9] in patients with chronic bronchitis.

Methods

PATIENTS AND STUDY DESIGN

Ten male hospital patients, aged from 50 to 72 years, with chronic bronchitis were selected for this study after their consent had been obtained. All patients at the start of the study were producing ample quantities of sputum throughout the day, and none had received treatment with antibiotics or mucolytic agents during the previous five days. There was no evidence of pneumonic consolidation on the chest radiograph of any patient.

Each patient received an eight-day course of erythromycin stearate (Erythrocin, Abbott Australasia Pty Ltd, C946, 250 mg capsule-shaped tablets), administered as a 500 mg dose orally at eight-hour intervals. The doses each day were given at 0800, 1600, and 2400 hours, with the first two doses each day taken immediately before food. During the study supportive treatment with aerosol bronchodilators and physiotherapy was continued as indicated at regular intervals.

Venous blood samples were taken at 0, 0·5, 1, 1·5, 2, 4, 6, and 8 hours after drug administration (0800 hours) on days 1, 3, and 8. Sputum was collected in plastic containers and for each period the purulence of the specimens was classified according to the following scheme[6]: *mucopurulent*=75% pus or more; 50% pus; 25% pus; trace of pus; *mucoid*=no pus.

Sputum specimens were obtained on the day before the start of the study, and after the 0800 hours drug administration on days 1, 3, and 8

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for the following periods: 0–2, 2–4, 4–6, 6–8, and 8–24 hours. For the other study days (2, 4, 5, 6, and 7), a 24-hour specimen was collected. Each sputum sample was assayed for erythromycin concentration. Sputum collected on the days before and after the study was cultured on appropriate media for common respiratory pathogens.

ASSAY METHOD FOR ERYTHROMYCIN CONCENTRATION

The assay method for plasma and sputum erythromycin followed that described by Bell *et al*[10] using a microbiological technique with *Sarcina lutea* ATTC 9341 as test organism. The sputum samples were prepared for assay by homogenising with N-acetyl-cysteine. The only modification to the method was the use of large 12×12 inch antibiotic assay plates which enabled six standards and 12 samples to be set on each plate. Each standard and sample was set twice, each assay plate being done in duplicate. Individual levels were obtained using linear regression of log concentration against zone diameter. The plasma and sputum levels in the results were the weighted means of the results from the two plates. Standard solutions of erythromycin were prepared using 3·5% bovine albumin and phosphate buffer pH 8·0 as diluent.

Results

The mean ±SD plasma erythromycin levels for all the patients during the first, third, and eighth days of erythromycin treatment are shown in table 1. The individual and mean ±SD peak plasma erythromycin levels (Cmax) and the times at which these peak levels occurred (tmax) on the first, third, and eighth days of erythromycin treatment are shown in table 2. A summary of the sputum purulence classification and sputum culture before and immediately after erythromycin treatment is shown in table 3. Although all patients were producing copious quantities of sputum at the beginning of the study, they were not always able to produce sputum during every collection period. Erythromycin was not always detected in the sputum specimens obtained. Table 4 demonstrates the number of samples obtained for all the time periods for the 10 patients and the number of specimens in which erythromycin was detected. The mean ±SD sputum erythromycin concentrations in those specimens in which the drug was detected for all the time periods are shown in table 4.

Plasma and sputum erythromycin levels were compared during the eight-hour period after the morning dose on the first, third, and eighth day.

Table 1 *Mean ± SD plasma erythromycin levels for the 10 patients before and at various times after 500 mg erythromycin stearate administered orally immediately before food (0800 hours) on days 1, 3, and 8 of an eight-day course (500 mg eight hourly)*

	Time (h)							
	0	*0·5*	*1*	*1·5*	*2*	*4*	*6*	*8*
Day 1	0	2·45±3·19	3·26±2·60	3·81±2·59	2·77±2·15	1·44±1·08	0·80±0·66	0·41±0·34
Day 3	1·48±1·37	5·17±3·70	4·87±2·93	4·87±2·30	4·76±2·57	3·14±1·78	2·43±1·59	1·60±1·24
Day 8	0·97±0·93	3·11±2·81	4·12±3·00	4·56±3·56	4·28±2·74	3·43±2·69	2·07±1·73	1·24±1·13

Plasma erythromycin levels: μg/ml. 1 μg/ml = 1/36 μmol l^{-1}.

Table 2 *Individual and mean ± SD peak plasma erythromycin levels (Cmax) and the times at which these levels occurred (tmax) for the 100 patients after 500 mg erythromycin stearate administered orally immediately before food (0800 hours) on days 1, 3, and 8 of an eight-day course (500 mg eight hourly)*

Patient	*Cmax (μg/ml)*			*tmax (h)*		
	Day 1	*Day 3*	*Day 8*	*Day 1*	*Day 3*	*Day 8*
1	1·59	2·91	2·70	2	0·5	6
2	6·42	2·31	1·22	1	2	2
3	1·32	8·45	1·60	1	1	1·5
4	1·30	3·74	3·29	1·5	1·5	1·5
5	7·28	8·39	12·28	1·5	0·5	1·5
6	1·70	4·54	3·06	1·5	0·5	0·5
7	6·70	4·29	7·13	1	1	2
8	9·52	13·19	7·75	0·5	0·5	0·5
9	5·00	7·34	6·34	1·5	1·5	2
10	1·12	6·73	6·54	1·5	1·5	2
Mean	4·20	6·19	5·19	1·30	1·05	1·95
SD	3·14	3·31	3·44	0·42	0·55	1·54

Erythromycin: 1 μg/ml = 1·36 μmol l^{-1}.

Table 3 *Amount of pus in the sputum and the sputum culture report for the 10 patients before and after an eight-day course of erythromycin stearate (500 mg eight hourly)*

Patient	*Before treatment*		*After treatment*	
	Amount of Pus	*Sputum culture*	*Amount of Pus*	*Sputum culture*
1	50%	Commensals	25%	Commensals
2	25%	Commensals	25%	Commensals
3	50%	Commensals	Trace	Commensals
4	25%	Commensals	Trace	Commensals
5	25%	*H Influenzae*	50%	Commensals
6	50%	Commensals	25%	Commensals
7	75%	*S Pneumoniae*	25%	Commensals
8	50%	*H Influenzae*	25%	Commensals
9	Trace	Pseudomonas Species	25%	Commensals
10	25%	Commensals	Trace	Commensals

Classification of sputum purulence: no pus; trace; 25%; 50%; 75% or more.

The plasma levels were averaged during each two-hour time period and tabulated in four groups according to the concentration: $<1{\cdot}0$, 1–3, 3–5, and >5 μg/ml. These results comparing plasma and sputum levels are shown in table 5. The mean ±SD plasma erythromycin level for patients when no erythromycin was detected in sputum was $1{\cdot}92 \pm 1{\cdot}91$ μg/ml ($2{\cdot}61 \pm 2{\cdot}60$ μmol l^{-1}), and $3{\cdot}58 \pm 2{\cdot}53$ μg/ml ($4{\cdot}87 \pm 3{\cdot}44$ μmol l^{-1}) when there were measurable sputum erythromycin levels. There was no positive correlation between plasma and sputum erythromycin levels ($r=0{\cdot}24$, $p>0{\cdot}05$). The relationship between sputum purulence and sputum erythromycin levels is shown in table 6. There were no unwanted effects reported during the study.

Table 5 *Relationship between the plasma and sputum erythromycin levels for the 10 patients during an eight-day course of erythromycin stearate (500 mg eight hourly). Plasma levels were averaged for each sputum collection period and grouped according to range of concentration for each patient. The mean ± SD sputum erythromycin levels are recorded for those samples in which erythromycin was detected*

Plasma erythromycin (μg/ml)	*Number of samples erythromycin not detected*	*Number of samples erythromycin detected*	*Mean ± SD sputum erythromycin (μg/ml)*
$<1{\cdot}00$	21	8	$0{\cdot}13 \pm 0{\cdot}10$
1·01—3·00	14	20	$0{\cdot}24 \pm 0{\cdot}22$
3·01—5·00	7	11	$0{\cdot}30 \pm 0{\cdot}26$
$>5{\cdot}00$	4	16	$0{\cdot}40 \pm 0{\cdot}55$

Erythromycin 1 μg/ml = 1·36 μmol l^{-1}.

Table 6 *Relationship between sputum purulence and sputum erythromycin levels for the 10 patients during an eight-day course of erythromycin stearate (500 mg eight hourly). The mean ± SD sputum erythromycin levels are recorded for those samples in which erythromycin was detected*

Sputum purulence	*Number of samples erythromycin not detected*	*Number of samples erythromycin detected*	*Mean±SD sputum erythromycin (μg/ml)*
No Pus	5	1	0·20
Trace	33	38	$0{\cdot}26 \pm 0{\cdot}38$
25%	30	39	$0{\cdot}22 \pm 0{\cdot}14$
50%	7	11	$0{\cdot}43 \pm 0{\cdot}34$
75% or more	0	0	—

Erythromycin 1 μg/ml = 1·36 μmol l^{-1}.

Table 4 *Sputum results for the 10 patients for the various collection periods during an eight-day course of erythromycin stearate (500 mg eight hourly)*

Day	*Hours*	*Number of patient samples*	*Number of samples erythromycin not detected*	*Number of samples erythromycin detected*	*Mean + SD (μg/ml)*
1	0–2	9	5	4	$0{\cdot}10 \pm 0{\cdot}02$
	2–4	10	4	6	$0{\cdot}26 \pm 0{\cdot}37$
	4–6	9	7	2	$0{\cdot}56 \pm 0{\cdot}71$
	6–8	9	7	2	$0{\cdot}23 \pm 0{\cdot}21$
	8–24	10	3	7	$0{\cdot}27 \pm 0{\cdot}16$
2	0–24	10	3	7	$0{\cdot}23 \pm 0{\cdot}24$
3	0–2	10	3	7	$0{\cdot}24 \pm 0{\cdot}18$
	2–4	7	2	5	$0{\cdot}29 \pm 0{\cdot}16$
	4–6	8	3	5	$0{\cdot}60 \pm 0{\cdot}81$
	6–8	8	3	5	$0{\cdot}22 \pm 0{\cdot}13$
	8–24	9	3	6	$0{\cdot}24 \pm 0{\cdot}12$
4	0–24	9	4	5	$0{\cdot}19 \pm 0{\cdot}07$
5	0–24	8	5	3	$0{\cdot}25 \pm 0{\cdot}04$
6	0–24	8	3	5	$0{\cdot}14 \pm 0{\cdot}08$
7	0–24	9	3	6	$0{\cdot}23 \pm 0{\cdot}16$
8	0–2	9	4	5	$0{\cdot}14 \pm 0{\cdot}07$
	2–4	7	3	4	$0{\cdot}52 \pm 0{\cdot}63$
	4–6	9	4	5	$0{\cdot}21 \pm 0{\cdot}09$
	6–8	8	3	5	$0{\cdot}21 \pm 0{\cdot}12$
	8–24	8	2	6	$0{\cdot}23 \pm 0{\cdot}12$

Erythromycin: 1 μg/ml = 1·36 μmol l^{-1}.

Discussion

This study demonstrates consistent gastrointestinal absorption of this erythromycin stearate formulation administered immediately before food during an eight-day treatment course in patients with chronic bronchitis. The erythromycin plasma levels achieved compare favourably with the minimal inhibitory concentrations for common respiratory pathogens—for example, beta-haemolytic *Streptococcus* (0·02–0·2 μg/ml) (0·03–0·27 μmol l^{-1}), *Streptococcus pneumoniae* (0·01–0·2 μg/ml) (0·01–0·2 μmol l^{-1}), *Staphylococcus aureus* (0·01–1·6 μg/ml) (0·01–2·18 μmol l^{-1}), *Haemophilus influenzae* (0·4–3·0 μg/ml) (0·54–4·08 μmol l^{-1}), and *Mycoplasma pneumoniae* (0·005–1·5 μg/ml) (0·007–2·04 μmol l^{-1}).[4 7 11]

There was considerable individual variability and a wide range of erythromycin levels in bronchial secretions, a finding observed with other antibiotics—for example, penicillin,[12] ampicillin,[13-15] amoxycillin,[16 17] tetracyline and its derivatives.[18-20] The range of sputum erythromycin levels was generally low, reaching a maximum of 2·02 μg/ml (2·74 μmol l^{-1}), and in five patients erythromycin was consistently undetectable in sputum, only present in fewer than five specimens. Measurable sputum erythromycin levels were approximately 10% of plasma levels throughout the study with no evidence of accumulation (tables 4 and 5). Although there was a trend for sputum erythromycin levels to increase with plasma levels, no positive correlation was found. This would indicate that processes other than simple diffusion might be involved in the passage of erythromycin into sputum. The sputum erythromycin concentrations achieved were of a similar order of magnitude to the minimal inhibitory concentrations for common respiratory pathogens with the exception of that for *Haemophilus influenzae*. The bronchial mucosa is the site of infection in acute exacerbations of chronic bronchitis.[21] Although it is assumed that a gradient of concentration of antibiotic exists from blood through bronchial mucosa to bronchial secretions, sputum concentrations may not always reflect tissue levels. Antibiotics excreted into bronchial secretions will be diluted to a degree dependent upon the volume of mucus within the bronchial tree and this may lead to variability of antibiotic concentrations. The eradication of bronchial infection is more likely to depend upon the bronchial tissue antibiotic concentration than on the sputum concentration. In this study, in seven patients sputum purulence was reduced during the course of treatment indicating that bronchial tissue erythromycin levels may have been adequate (table 3). However, although all patients presented with sputum containing pus, bacterial pathogens were only isolated in four patients. This may reflect previous antibiotic therapy, although no patient received antibiotics during the five days before the study. In two patients, sputum purulence increased despite the organisms being eliminated on sputum culture. *Pseudomonas* species was present initially in one of these patients, which again may reflect previous antibiotic therapy, and improvement would not be expected with erythromycin, to which this organism is resistant. There was a trend for higher erythromycin levels in sputum containing increasing amounts of pus (table 6). This may indicate that the transfer of erythromycin into sputum is facilitated by the presence of pus, such as occurs with ampicillin[15] and amoxycillin.[17] Acute infection leads to vasodilatation and in the bronchial mucosa increased vascular permeability for antibiotics may result. There are many natural defence mechanisms in the bronchial tree which play a role in the eradication of infection. This study was not specifically designed to examine the efficacy of erythromycin in acute bronchial infections, when double-blind, placebo-controlled conditions would be required. Thus, no conclusions should be drawn from the results of erythromycin treatment in this study.

Neaverson[22] measured serum and spot sputum erythromycin levels in five patients with lower respiratory tract infections during a five-day course of erythromycin lactobionate administered by continuous intravenous infusion and found a range of sputum levels from 0·9 to 8·4 μg/ml (1·2 to 11·4 μmol l^{-1}) with peak serum levels similar to those in the present study. However, a constant steady-state serum erythromycin level would be expected with this method of administration compared with the fluctuating levels after oral intake and this would explain the higher sputum concentrations. Recently, Simon and Clasen[23] have demonstrated a similar range of sputum erythromycin levels compared with the present study in patients with bronchial disease during four days of oral treatment, although serum levels achieved were lower. Frashini *et al*,[24] however, have found higher sputum erythromycin levels in patients with bronchial disease over a 24-hour period, and the levels tended to increase with time suggesting either accumulation in pulmonary tissue or in the bronchial lumen overnight.

This work demonstrates adequate gastrointes-

tinal absorption of a new erythromycin stearate formulation when administered immediately before food. If plasma levels are a guide to tissue antibiotic levels, erythromycin would appear to be a suitable antibiotic for the treatment of acute, infective exacerbations of chronic bronchitis. The concentration of erythromycin in bronchial secretions, however, was variable and in some patients low or undetectable. Sputum antibiotic concentration may be relevant for the long-term suppression of bacterial growth in the bronchial tree in patients who have frequent relapses of acute bronchial infection and for such therapy the value of erythromycin may be limited. Further clinical trials are required to assess the efficacy of adequately absorbed erythromycin formulations compared with placebo and other antibiotics in the treatment of acute bronchial infections.

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