

Concentrations of cefixime in bronchial mucosa and sputum after three oral multiple dose regimens

David R Baldwin, Jennifer M Andrews, Janet P Ashby, Richard Wise, David Honeybourne

Abstract

In a study of 58 patients the concentrations of cefixime, a new oral cephem antibiotic, in bronchial mucosa were 35-40% of the concentrations found in simultaneously collected serum samples. The antibiotic was often undetectable in sputum despite a highly sensitive assay.

The likely efficacy of an antimicrobial in the treatment of chest infections may be assessed by measuring the concentrations of the drug in sputum and bronchial mucosa after administration as these are the potential sites of infection.¹⁻³

Cefixime is a new oral cephem antibiotic with a relatively long half life and in vitro activity similar to those of the third generation cephalosporins, currently available only for parenteral use.⁴

We report the concentrations of cefixime in serum, sputum, and bronchial mucosa after oral administration of cefixime for three days.

Methods

The 58 patients studied fell into two groups, according to whether bronchial mucosa or sputum was sampled. Patients in each group were given one of three dosage regimens of cefixime according to a random allocation (table 1). Patients in the bronchial mucosa groups were undergoing fiberoptic bronchoscopy for diagnostic purposes.

Exclusion criteria included clinical or laboratory evidence of appreciable cardiac, renal, or hepatic impairment; active lung infection; pregnancy and lactation; hypersensitivity to β lactam drugs; and the administration of other antimicrobial agents in the two previous weeks.

All patients gave informed written consent and the study was approved by the local hospital ethical committee.

Bronchoscopy was performed after premedication with 0.6 mg intramuscular atropine, 160 mg nebulised 4% lignocaine and intravenous midazolam as sedation. Biopsy specimens were taken from macroscopically normal subcarinae and placed in a humidity chamber. A blood sample was taken at the same time as the mucosal biopsy or sputum sample. Bronchial biopsy specimens were placed in chilled phosphate buffer and ultrasonicated on ice for two minutes at 50% duty cycle (W225 Sonicator 1 Heat Systems Ultrasonics Inc).

All specimens were analysed by means of a microbiological plate diffusion technique in which the indicator strain (*Providentia stuartii* K166 Dudley Road Hospital) was inoculated on to pre-poured plates of Antibiotic No 1 medium (Oxoid CM327, Basingstoke). Assay plates were incubated at 37°C for 18 hours. The between assay coefficient was 7.4% and the lower limit of sensitivity was 0.015 mg/l.

The percentage penetration into tissue was defined as

$$\frac{\text{tissue concentration}}{\text{serum concentration}} \times 100.$$

Statistical comparisons were performed by paired *t* test.

Results

The concentration of cefixime in 13 of the 28 sputum samples was below the sensitivity of the assay; this occurred with sputum from patients from all three drug regimens (table 2). Cefixime was undetectable in only one sample of bronchial mucosa. The undetectable concentrations were excluded in the calculation of mean values. The differences in cefixime concentrations between sputum and mucosa were highly significant for two regimens—400 mg daily ($p < 0.001$) and 200 mg twice daily ($p = 0.003$). Only three patients taking 200 mg daily had measurable cefixime concentrations in sputum, so analysis was not possible for this regimen.

Discussion

After oral doses in all three dosage groups of cefixime we found that the bronchial mucosal

Department of Thoracic Medicine

D R Baldwin
D Honeybourne

Department of Medical Microbiology, Dudley Road Hospital, Birmingham

J M Andrews
J P Ashby
R Wise

Address for reprint requests:
Dr D R Baldwin, Dudley
Road Hospital, Birmingham
B18 7QH.

Accepted 18 January 1990

Table 1 Dose regimens for cefixime, given for three days before sampling of sputum or bronchial mucosa

Group	No of patients	Sample	Dose	
A	9	Sputum	200 mg	} daily
B	10	Bronchial mucosa	200 mg	
C	9	Sputum	200 mg	} twice daily
D	10	Bronchial mucosa	200 mg	
E	10	Sputum	400 mg	} daily
F	10	Bronchial mucosa	400 mg	

Table 2 Cefixime concentrations, with details of samples and time of last dose, in the six groups of patients (mean (SD) unless otherwise specified)

	Dose regimen					
	200 mg daily		200 mg twice daily		400 mg daily	
	Sputum 9	Mucosa 10	Sputum 9	Mucosa 10	Sputum 10	Mucosa 10
No of patients:						
Serum concentration (mg/l)	2.3 (2.0)	3.9 (1.3)	3.2 (1.4)	4.6 (2.6)	4.2 (2.3)	6.6 (2.5)
Sputum or mucosa concentration (mg/l)	0.02 (0.05)	1.5 (0.6)	0.02 (0.02)	1.6 (1.1)	0.07 (0.1)	2.4 (0.9)
Hours since last dose	2.5 (1.6)	3.9 (0.9)	3.5 (1.6)	3.8 (0.6)	2.7 (1.2)	4.3 (0.6)
Biopsy sample weight (mg)						
Mean	6.5		9.4		6.7	
Range		4.3-9.7		4.7-14.3		4-11.5
SD		(2.0)		(3.2)		(2.2)
No of samples with undetectable concentrations	6	1	5	0	2	0

concentrations of cefixime were far higher than the sputum concentrations.

The low sputum concentrations should be interpreted in the light of recognised difficulties in the measurement of antimicrobials in sputum. Sputum pooling and contamination with saliva or blood may partly explain the inconsistent and variable concentrations previously measured in sputum.^{5,6} Attempts have been made to avoid this problem by sampling secretions directly from endotracheal and tracheostomy tubes, or at fiberoptic bronchoscopy. Even when contamination with blood and saliva is minimised, however, the problem of sputum pooling remains.

Sputum pooling means that the antibiotic measured may represent an average of the concentrations at different sites and at different times. Pooling of secretions allows time for loss of antibacterial activity due to instability of the compound brought about by changes in temperature, pH, or protein content.⁷

Histological studies suggest that infection may occur in both the sputum and the bronchial mucosa in an acute exacerbation of chronic bronchitis or bronchiectasis.^{8,9} There is also evidence that bacteria attach themselves to bronchial mucosal surfaces,¹⁰ probably by means of protein structures in the fimbriae of the bacterial cell wall termed adhesins.¹¹ The presence of fibronectin on the host cell surface favours adhesion of some bacteria, especially streptococci. This may be relevant to the action of β lactam antibiotics as the latter appear to decrease the binding of bacteria to fibronectin.¹² The likely clinical efficacy therefore may be reflected better by antimicrobial activity measured in bronchial mucosa than by the activity measured in sputum; clinical trials would be required to confirm this, however.

The concentrations of cefixime found in

bronchial mucosa exceeded the MIC₉₀ values (the minimum concentration inhibiting 90% of strains of pathogens) for the common pathogens associated with exacerbations of chronic bronchitis (table 3). Cefixime may therefore have a role in the treatment of this condition.

Table 3 MIC₉₀ of cefixime for common respiratory pathogens*

Organism	MIC ₉₀ (mg/l)
<i>Streptococcus pneumoniae</i>	0.12
<i>Haemophilus influenzae</i>	
Ampicillin sensitive	0.03
Ampicillin resistant	0.12
<i>Branhamella catarrhalis</i>	0.12

*R Wise and JM Andrews, unpublished data.

MIC₉₀—minimum concentration inhibiting 90% of strains of pathogens in vitro.

- Marlin GE, Burgess J, Burgoyne J, Furrell GR, Guinness MDG. Penetration of piperacillin into bronchial mucosa and sputum. *Thorax* 1981;36:774-80.
- Honeybourne D, Andrews JM, Ashby JP, Lodwick R, Wise R. Evaluation of the penetration of ciprofloxacin and amoxicillin into the bronchial mucosa. *Thorax* 1988; 43:715-9.
- Thadepalli H. Lower respiratory tract. In: Ristuccia AM, Cunha BA, eds. *Antimicrobial therapy*. New York: Raven, 1984:439-54.
- Bauernfeind A. A new generation of oral cephalosporins: cefixime (FK027) in vitro activity against isolates from West Germany. In: *Proceedings of workshop of 14th International Congress on Chemotherapy*. Kyoto, 1985:11-6.
- Bergogne-Berezin E. Penetration of antibiotics into the respiratory tree. *J Antimicrob Chemother* 1981;8:171-4.
- Pennington JE. Penetration of antibiotics into respiratory secretions. *Rev Inf Dis* 1981;3:67-73.
- Marlin GE, Nicholls AJ, Funnell GR, Bradbury R. Penetration of cefaclor into bronchial mucosa. *Thorax* 1984;39:813-7.
- Hers JGP, Mulder J. The mucosal epithelium of the respiratory tract in mucopurulent bronchitis caused by *Haemophilus influenzae*. *J Pathol Bacteriol* 1953;66:103-8.
- Palmer LB. Bacterial colonisation: pathogenesis and clinical significance. *Clin Chest Med* 1987;8:455-66.
- Anonymous. What makes microbes stick? [editorial]. *Lancet* 1988;ii:1343-4.
- Duguid JP, Clegg S, Wilson MI. The fimbrial and non-fimbrial haemagglutinins of *Escherichia coli*. *J Med Microbiol* 1979;12:213-7.
- Wood DE. Role of fibronectin in the pathogenesis of gram-negative bacillary pneumonia. *Rev Inf Dis* 1987;S:386-90.