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The in vitro effects of faropenem on lower respiratory tract pathogens isolated in the United Kingdom

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Abstract

Faropenem is a new oral penem with a structure different from current β-lactams including carbapenems. The susceptibility of *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis* to faropenem, a macrolide, a β-lactam, a β-lactam/β-lactamase inhibitor combination and two fluoroquinolones was investigated. *S. pneumoniae* was the most susceptible of the three species to faropenem. The MIC_{90}s of faropenem against *M. catarrhalis* and *H. influenzae* were 0.5 and 1 mg/l, respectively. They were similar to amoxiclav (MIC $_{90}$s of 0.25 and 0.5 mg/l). The quinolones showed strong activity against *H. influenzae*. A cluster analysis of the activities of amoxycillin and faropenem demonstrated a direct relationship between the two antimicrobial agent's activities and resistance profiles against both *S. pneumoniae* and *H. influenzae*.

Keywords: Faropenem; *Streptococcus pneumoniae*; MIC

1. Introduction

Faropenem is a new oral penem antimicrobial agent, which has an unsaturated thiazole ring and is a structural hybrid between the penicillin and carbapenem nucleus (Fig. 1). It is characterised by potent penicillin binding protein activity and β-lactamase stability. The antibacterial spectrum of faropenem includes Gram-positive, Gram-negative and some anaerobic bacteria [1]. In common with other β-lactams, target modifications via altered penicillin-binding proteins (PBPs) have previously been shown to increase the minimum inhibitory concentration (MIC) of faropenem for respiratory tract infections compared with wild type strains [2].

Faropenem typically shows high affinity for PBPs compared with other agents. Respiratory tract infections are a major cause of morbidity and mortality in the community and hospitals. *Streptococcus pneumoniae*, *Moraxella catarrhalis* and *Haemophilus influenzae* are common causes of lower respiratory tract infections (LRTIs) and upper respiratory tract infections (URTIs). Worldwide, the annual incidence of community-acquired pneumonia (CAP) is estimated to be 1.1–4.0 per 1000 population. In the UK CAP accounts for 5–12% of cases of LRTIs among adults approximately 20–42% of which require hospitalisation [3].

This study compared the in vitro activity of faropenem against *S. pneumoniae*, *M. catarrhalis* and *H. influenzae* isolated in the UK with amoxycillin, amoxiclav, clarithromycin, levofloxacin and ciprofloxacin activity.

2. Materials and methods

2.1. Antimicrobial agents

The following antimicrobial agents were studied: faropenem and ciprofloxacin (Bayer), amoxycillin (CP Pharmaceuticals), amoxiclav (SmithKline Beecham Pharmaceuticals and CP Pharmaceuticals), clarithromycin (Abbott) and levofloxacin (Aventis Pharma Ltd.). The antimicrobial agents were stored and prepared according to the suppliers' instructions. The amoxiclav

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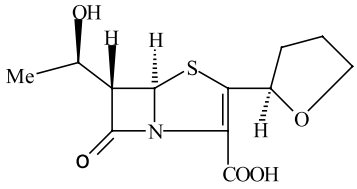

Fig. 1. Faropenem chemical structure.

consisted of fixed concentrations of 2 mg/l of clavulanic acid per plate and doubling dilutions of amoxycillin [4].

2.2. Bacterial strains

S. pneumoniae ($n = 100$) from Edinburgh and Leeds, *M. catarrhalis* (100) from Edinburgh, Leeds and Wales and *H. influenzae* (100) from Edinburgh and Glasgow, collected between 1997 and 2000, were used in this study. The control strains comprised *S. pneumoniae* NCTC 13593, *Staphylococcus aureus* NCTC 6571, *H. influenzae* NCTC 11931 and a laboratory reference strain of *M. catarrhalis*.

2.3. Susceptibility testing

MICs were determined by standard agar dilution methods according to the BSAC guidelines for sensitivity testing [4] on Columbia agar (Oxoid, Basingstoke) supplemented with 5% defibrinated horse blood for *S. pneumoniae* and *M. catarrhalis* and chocolate Columbia agar plates for *H. influenzae*.

A final concentration of 10^5 cfu per spot of *S. pneumoniae* and 10^4 cfu per spot of *H. influenzae* and *M. catarrhalis* were inoculated onto each plate. The plates were incubated aerobically.

3. Results

The MICs of faropenem and the comparators are given in Table 1.

For *S. pneumoniae*, faropenem had the lowest MIC_{50} (0.008 mg/l) and MIC_{90} (0.25 mg/l) of all the antimicrobial agents tested. The faropenem modal MIC against *S. pneumoniae* was 0.008 mg/l for 39 isolates, which was also the lowest concentration compared with 0.016 mg/l (37 isolates) for amoxiclav, 0.016–0.032 mg/l for amoxycillin against 70 isolates, 0.032 mg/l (42 isolates) for clarithromycin and 1 mg/l for both levofloxacin (48 isolates) and ciprofloxacin (28 isolates).

Faropenem had the second largest MIC_{90} and the second highest range endpoint against *M. catarrhalis*. The quinolones levofloxacin and ciprofloxacin had the lowest MIC_{90}s at 0.06 mg/l. The modal MICs of faropenem were 0.06 mg/l, for 27 isolates and 0.25 mg/l for 25 isolates of *M. catarrhalis*. Levofloxacin and ciprofloxacin inhibited 66 and 73 strains of *M. catarrhalis*, respectively, at 0.032 mg/l. The mode MIC of clarithromycin was 0.12 mg/l, which inhibited 54 isolates. Amoxiclav did not have a mode concentration against *M. catarrhalis*. Amoxiclav inhibited 17 isolates at 0.004, 0.008 and 0.6 mg/l; 16 isolates had amoxiclav MICs of 0.12 mg/l, 12 isolates had MICs of 0.002 mg/l, nine had MICs of 0.25 mg/l, eight were inhibited by 0.032 mg/l and four isolates were inhibited by 0.016 mg/l. The mode concentration of amoxycillin was between 1 and 4 mg/l and inhibited 61 isolates.

The MIC_{50} and MIC_{90} of faropenem for *H. influenzae* were 0.5 and 1 mg/l, respectively. Clarithromycin had an MIC_{50} and MIC_{90} of 4 and 8 mg/l. Both quinolones had MIC_{50} and MIC_{90}s of six doubling dilutions lower than faropenem. However, the results of faropenem were

Table 1
MIC values of the antimicrobial agents

Organism (number)	Antimicrobial agent	MIC_{50} (mg/l)	MIC_{90} (mg/l)	Range (mg/l)	Mode MIC (mg/l), [number of strains]
S. pneumoniae (100)	Faropenem	0.008	0.25	0.002–1	0.008 [39]
	Amoxycillin	0.032	0.5	0.004–2	0.016 [36]/0.032 [34]
	Amoxiclav	0.016	0.5	0.004–2	0.016 [37]
	Clarithromycin	0.06	2	0.008– > 32	0.032 [42]
	Levofloxacin	1	2	0.12–2	1 [48]
	Ciprofloxacin	1	4	0.032–8	1 [28]
M. catarrhalis (100)	Faropenem	0.12	0.5	0.032–1	0.06 [27]/0.25 [25]
	Amoxycillin	1	4	0.016–8	1 [16]/2 [20]/4 [25]
	Amoxiclav	0.016	0.25	0.002–0.25	0.004 [17]/0.008 [17], 0.06 [17]/0.12 [16]
	Clarithromycin	0.12	0.12	0.032–0.25	0.12 [54]
	Levofloxacin	0.032	0.06	0.016–0.12	0.032 [66]
	Ciprofloxacin	0.032	0.06	0.016–0.06	0.032 [73]
H. influenzae (100)	Faropenem	0.5	1	0.06–4	0.5 [48]
	Amoxycillin	0.5	4	< 0.032–32	0.5 [50]
	Amoxiclav	0.25	0.5	0.016–2	0.25 [33]/0.5 [40]
	Clarithromycin	4	8	< 0.06–16	8 [36]
	Levofloxacin	0.008	0.016	0.004–1	0.008 [43]
	Ciprofloxacin	0.008	0.016	< 0.004–2	0.008 [66]

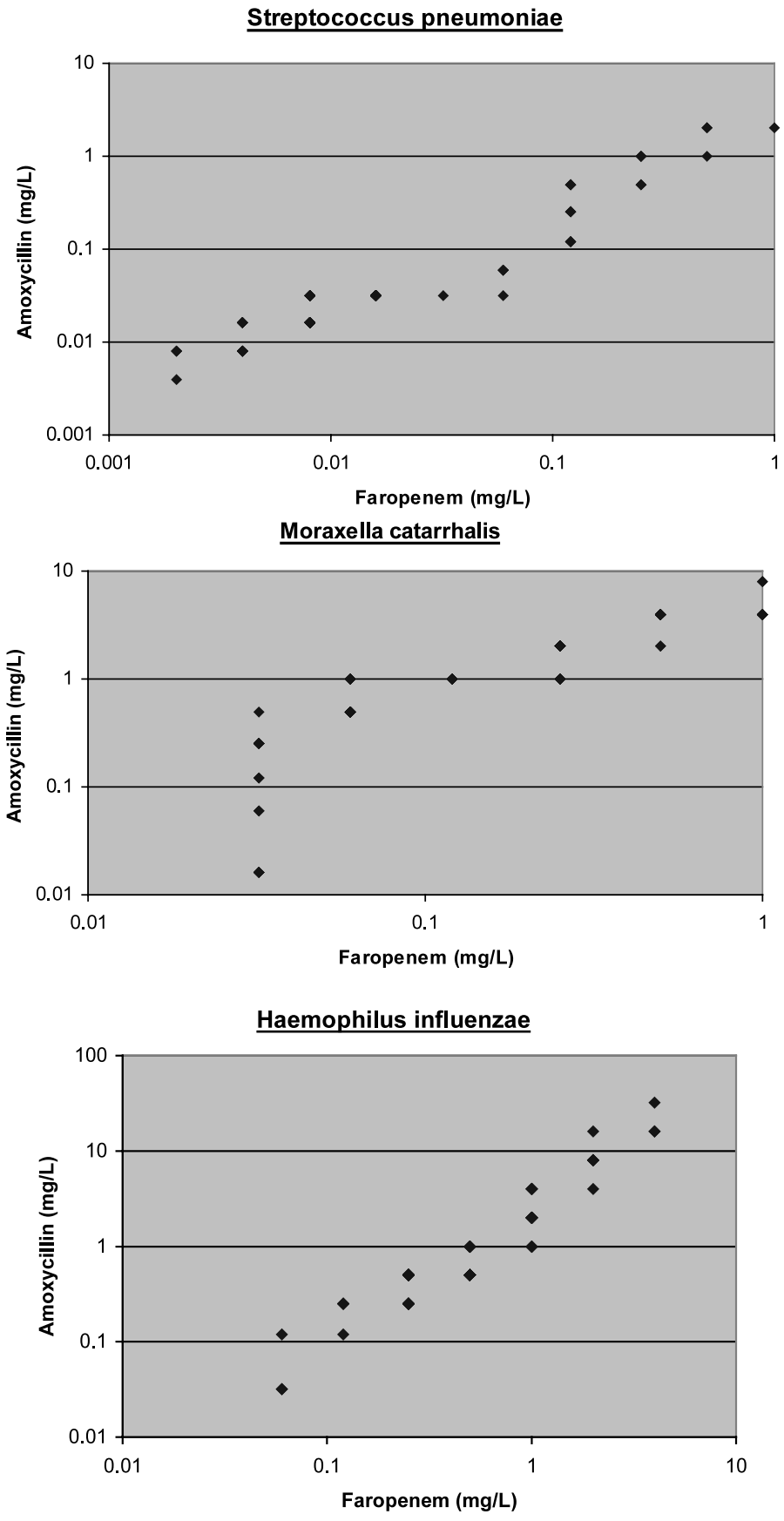

Fig. 2. Cluster analysis of amoxycillin and faropenem activity.

comparable with amoxiclav, which had lower MIC_{50} and MIC_{90} values than faropenem, but only by one doubling dilution. The MIC_{50} and MIC_{90} of amoxycillin against *H. influenzae* were 0.5 and 4 mg/l, respectively. The mode MIC of faropenem for *H. influenzae* was 0.5 mg/l for 48 isolates compared with 0.008 mg/l for levofloxacin and ciprofloxacin against 43 and 66 isolates, respectively.

The results suggest that there might be a direct correlation between the sensitivity to amoxycillin and to faropenem. So a cluster analysis of faropenem and amoxycillin MICs against *S. pneumoniae*, *M. catarrhalis* and *H. influenzae* was performed (Fig. 2). The two graphs have the same distribution patterns and both indicate that there is a direct relationship between amoxycillin and faropenem inhibition of *S. pneumoniae* and *H. influenzae*. As resistance to amoxycillin increases, there is a proportional increase in resistance to faropenem. The correlation with *M. catarrhalis* is less pronounced and does not occur until high levels of penicillin resistance are reached. Thus, strains of *S. pneumoniae* and in many cases, *H. influenzae* isolates, resistant to amoxycillin due to alterations in penicillin binding proteins are also able to confer resistance to faropenem [7]. Those strains where β-lactamase resistance is more prominent, particularly *M. catarrhalis* show less resistance to faropenem.

4. Discussion

The faropenem results obtained in this study agree with previously reported data and indicate that it has significant activity ($MIC_{90} \leq 1$ mg/l) against respiratory tract infections such as *S. pneumoniae*, *M. catarrhalis* and *H. influenzae* [5,6]. The activity of faropenem was usually of a similar level to that of amoxiclav. This is perhaps not surprising as the clavulanic acid component of amoxiclav removes the β-lactamase contribution to amoxycillin resistance and faropenem is β-lactamase stable. This is emphasised by the correlation between amoxycillin and faropenem inhibition shown in Fig. 2. These cluster analyses show a direct relationship between faropenem and amoxycillin sensitivities demonstrating that faropenem was not capable of over-coming the resistance mechanisms arising from alteration of penicillin binding proteins in *S. pneumoniae*. The correlation was also quite clear in *H. influenzae*, where much of the amoxycillin resistance is mediated by mechanisms other than β-lactamase hydrolysis [7]. There is less obvious correlation in *M. catarrhalis*, where β-lactamase hydrolysis is a more prominent mechanism of amoxycillin hydrolysis [8]. In this case, there is a major increase in amoxycillin resistance without a significant change in faropenem resistance. It is only after a threshold is reached that further increases in amoxycillin resistance correspond with concomitant increases in faropenem resistance. As anticipated the two quinolones tested had lower MIC_{50} and MIC_{90} values than all the agents tested for *H. influenzae* and all the agents except amoxiclav for *M. catarrhalis*. In these in vitro tests clarithromycin does not perform as well as faropenem against *S. pneumoniae* or *H. influenzae*. The results of faropenem demonstrate that it is a potent drug but these results suggest that the acquisition of penicillin resistance would have an adverse effect on faropenem in *S. pneumoniae* and *H. influenzae* but less so in *M. catarrhalis*.

Acknowledgements

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