IN VITRO ACTIVITY OF TEICOPLANIN, VANCOMYCIN, A16686, CLINDAMYCIN, ERYTHROMYCIN AND FUSIDIC ACID AGAINST ANAEROBIC BACTERIA

H Hassan, M D O'Hare, D Felmingham

ABSTRACT

The in vitro activity of teicoplanin and A16686, two new glycopeptide antibiotics was determined against 196 isolates of anaerobic bacteria. The activity of teicoplanin and A16686, in comparison with that of vancomycin, clindamycin, erythromycin and fusidic acid was 2 to 16 times higher against the gram positive anaerobes, namely, *Propionibacterium acnes, Clostridium perfringens, Clostridium difficile*, Clostridium species, Peptococcus species and Peptostreptococcus species. However, *Bacteroides fragilis* was resistant to teicoplanin and A16686 while *Bacteroides melaninogenicus* and *Bacteroides bivius* were found to be sensitive.

Keywords: Anaerobic organisms, Teicoplanin, A16686

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INTRODUCTION

The increasing awareness of resistance or adverse reactions among the commonly used antibiotics, which include clindamycin, metronidazole and chloramphenicol, against anaerobic bacteria provides an impetus for the search of new antibiotics that could be used as alternative treatment to the existing spectrum of antibiotics against the anaerobes.

Two new glycopeptide antibiotics derived from the fermentation of 2 different Actinoplanes species have recently been described. They are teicoplanin (1) and A16686 (2). Teicoplanin is a complex of 5 closely related molecules differing in the nature of fatty acids. It is related to the glycopeptide group of antibiotics, namely, vancomycin, ristomycins, ristocetin, the actinoridins and the manopeptidins. Its mechanism of action shows that it inhibits peptidoglycan synthesis in intact cells and cell free systems (3). A16686 is a complex of 3 closely related polypeptide containing chlorinated phenyl moieties. It causes rapid suppression of cell synthesis (4). Both have shown great activity against gram positive aerobes and anaerobes (5, 6). We explored the potential for these 2 investigational antibiotics and compared their activities with that of more established antimicrobial agents for both gram positive and gram negative anaerobes, namely, clindamycin, vancomycin, erythromycin and fusidic acid.

Department of Medical Microbiology
Faculty of Medicine
University of Malaya
59100 Kuala Lumpur
Malaysia

H Hassan, MBBS(Mal), MSc(Lond)
Lecturer

Department of Clinical Microbiology
University College Hospital
Grafton Way, London
United Kingdom

M D O'Hare, BSc, MSc (UK),
Senior Laboratory Scientific Officer

D Felmingham, BSc, MSc (UK)
Chief Medical Laboratory Scientific Officer

MATERIALS AND METHOD

ANTIBIOTICS

Teicoplanin and A16686 were supplied by Merrel Dow Pharm. The other reference antibiotics were obtained from the following firms: Vancomycin, Eli Lilly and Co. Ltd.; Clindamycin, Upjohn; Erythromycin, Abbot Laboratories; and Fusidic acid, Leo Ltd.

BACTERIAL STRAINS

196 isolates of anaerobic bacteria were collected from clinical specimens submitted to the Department of Clinical Microbiology, University College Hospital, London. The isolates were identified by API20A method and distributed as follows: 23 strains of *Bacteroides fragilis*, 25 strains of *Bacteroides melaninogenicus*, 12 strains of *Bacteroides bivius*, 4 strains of Fusobacterium species, 12 strains of Peptococcus species, 10 strains of Peptostreptococcus species, 25 strains of *Clostridium perfringens*, 25 strains of *Clostridium difficile*, 10 strains of Clostridium species and 50 strains of *Propionibacterium acnes*.

SUSCEPTIBILITY TEST

Isolates were tested for susceptibility by agar dilution method in Oxoid Isosensitest agar containing 5% lysed whole blood. The bacterial suspension was inoculated using Denley 100 multipoint inoculator. Inocula of 10^8 cfu/spot were delivered by the inoculator. The antibiotics were tested in twofold serial dilutions at concentrations ranging from 0.004 mg/L to 128 mg/L. The plates were incubated anaerobically at 37°C for 48 hours in an anaerobic cabinet. The MIC was read as the lowest concentration of antibiotic at which there is no visible growth.

Table I
COMPARATIVE IN-VITRO ACTIVITY OF ANTIBIOTICS AGAINST ANAEROBIC ORGANISMS.

	MIC_{90} (mg/L)					
Organism (No.)	**T**	**A**	**V**	**C**	**E**	**FA**
Clostridium perfringens (25)	0.06	0.12	0.5	2.0	1.0	2.0
Clostridium spp. (10)	1.0	0.12	1.0	0.5	1.0	0.5
Clostridium difficile (25)	0.12	0.5	1.0	0.25	1.0	0.25
Propionibacterium acnes (50)	0.25	0.25	0.5	0.25	0.03	1.0
Peptococcus spp. (12)	0.25	0.25	0.25	1.0	4.0	4.0
Peptostreptococcus spp. (10)	0.25	1.0	0.5	1.0	4.0	4.0
Bacteroides fragilis (23)	64	>128	64	2.0	2.0	8.0
Bacteroides melaninogenicus (25)	0.5	4.0	32	0.12	0.5	1.0
Bacteroides bivius (12)	1.0	2.0	64	0.12	1.0	4.0
Fusobacterium spp. (4)	64	>128	64	1.0	1.0	64

T = Teicoplanin, A = A16686, V = Vancomycin
C = Clindamycin, E = Erythromycin, FA = Fusidic Acid

RESULTS

The MIC_{90} of teicoplanin, A16686, vancomycin, clindamycin, erythromycin and fusidic acid for the anaerobic bacteria are presented in Table I. The results revealed that teicoplanin and A16686 are more active than other antibiotics against the gram positive anaerobes, including *Propionibacterium acnes*. They have little or no activity against the *Bacteroides fragilis* (MIC_{90} > 128 mg/L). However, the 2 new antibiotics showed great potential in their activities against *Bacteroides melaninogenicus* and *Bacteroides bivius* (Table I). The comparative activity of teicoplanin, A16686, vancomycin, clindamycin, erythromycin and fusidic acid against all 196 isolates are presented in Table I. It shows that teicoplanin and A16686 are potentially active against anaerobes at a lower concentration than the other antibiotics.

DISCUSSION

The result of this study showed that both teicoplanin and A16686 were active in vitro against the gram positive anaerobes. None of the isolates had MIC values greater than 1 mg/L for both teicoplanin and A16686. For teicoplanin, this value is below the mean serum level of 2.1 mg/L achieved 24 hours after a single intramuscular 3 mg/kg dose (7). Although the pharmacokinetics on humans for A16686 has not been established, it is probable that its mean serum level would be somewhat comparable to teicoplanin. These activities are comparable to that shown by vancomycin. Clindamycin, erythromycin and fusidic acid showed varying activities towards the gram positive anaerobic bacteria. The results of 4 studies done by different authors evaluating the activity of teicoplanin on gram positive anaerobes showed similar results as obtained in this study (5, 6, 8, 9).

Particularly impressive was the outstanding activity of teicoplanin and A16686 against *Clostridium difficile*. All strains were inhibited by <0.5 mg/L of both antibiotics. This definitely shows the potential of these 2 new antibiotics as an alternative to vancomycin in the treatment of pseudomembranous colitis. Vancomycin is minimally absorbed when given via the oral route to patients with colitis, therefore inhibitory concentration ranging from 300 mg/L to >1000 mg/L are easily achieved within the colonic lumen and inhibit both the organism and its production of toxins (10). Preliminary pharmacological studies on teicoplanin (8) confirmed the non-gastrointestinal absorption of the antibiotic. No such studies are yet available for A16686.

The activities of teicoplanin (MIC_{90} 64 mg/L) and A16686 (MIC_{90} > 128 mg/L) on *Bacteroides fragilis* are close to that of vancomycin (MIC90 64 mg/L). Therefore the treatment of choice for infections caused by this organism would still have to depend on clindamycin, metronidazole, cefoxitin and chloramphenicol. The scattered reports of *Bacteroides fragilis's* resistance to these antibiotics had initiated a more determined search for alternative treatments (11, 12). Teicoplanin and A16686 have promising activities on *Bacteroides melaninogenicus* and *Bacteroides bivius*. The discovery of the full potential of these antibiotics on these organisms would be most useful as the resistance among these organisms to penicillin which was used extensively for their treatment is ever increasing. Along with vancomycin and fusidic acid, teicoplanin and A16686 showed very little activity on Fusobacterium species. From various studies reported, the potential activity of teicoplanin is very promising indeed, especially against both gram positive aerobes and anaerobes (13). In comparison with vancomy-

cin, to which it shows much similarities in activity, teicoplanin's pharmacokinetics showed that it has a longer half-life in excess of 40 hours and this allows administration of a daily dose instead of several doses per day. Furthermore, it could be administered intramuscularly with no risk of tissue necrosis. It is also found to be well tolerated with mild and minimal adverse reactions.

The potential activity of A16686 is still being investigated but it has been found to be a potential anti-plaque agent because of its in vitro activity against *Streptococcus mutans* (14).

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