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To cite this version:

Noémi Anikó Bartha, József Sóki, Edit Urbán, Elisabeth Nagy. Investigation of the prevalence of , and genes in strains with elevated tigecycline minimum inhibitory concentrations. International Journal of Antimicrobial Agents, 2011, 38 (6), pp.522. 10.1016/j.ijantimicag.2011.07.010 . hal-00746419

HAL Id: hal-00746419

https://hal.science/hal-00746419v1

Submitted on 29 Oct 2012

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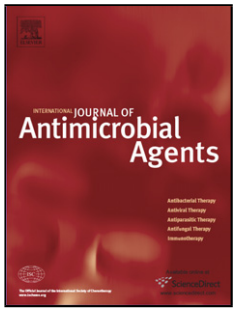

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PII: S0924-8579(11)00319-0
DOI: doi:10.1016/j.ijantimicag.2011.07.010
Reference: ANTAGE 3667

To appear in: *International Journal of Antimicrobial Agents*

Received date: 14-1-2011
Revised date: 19-3-2011
Accepted date: 9-7-2011

Please cite this article as: Bartha NA, Sóki J, Urbán E, Nagy E, Investigation of the prevalence of *tetQ*, *tetX* and *tetX1* genes in *Bacteroides* strains with elevated tigecycline minimum inhibitory concentrations, *International Journal of Antimicrobial Agents* (2010), doi:10.1016/j.ijantimicag.2011.07.010

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Investigation of the prevalence of *tetQ*, *tetX* and *tetX1* genes in *Bacteroides* strains with elevated tigecycline minimum inhibitory concentrations

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ARTICLE INFO

Article history:

Received 14 January 2011

Accepted 9 July 2011

Keywords:

Tigecycline

Bacteroides

tetX

tetX1

tetQ

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ABSTRACT

In this study, the antibiotic susceptibilities to tigecycline and tetracycline of 35 selected *Bacteroides fragilis* group strains were determined by Etest, and the presence of *tetQ*, *tetX*, *tetX1* and *ermF* genes was investigated by polymerase chain reaction (PCR). *tetQ* was detected in all 12 *B. fragilis* group isolates (100%) exhibiting elevated tigecycline minimum inhibitory concentrations (MICs) (≥8 μg/mL) as well as the 8 strains (100%) with a tigecycline MIC of 4 μg/mL, whilst *tetX* and *tetX1* were present in 15% and 75% of these strains, respectively. All of these strains were fully resistant to tetracycline (MIC ≥ 16 μg/mL). On the other hand, among the group of strains with tigecycline MICs < 4 μg/mL (15 isolates), *tetQ*, t*etX* and *tetX1* were found less frequently (73.3%, 13.3% and 46.7%, respectively). All but two strains harbouring the *tetQ* gene in this group were non-susceptible to tetracycline, with an MIC > 4 μg/mL. These data suggest that in most cases tigecycline overcomes the tetracycline resistance mechanisms frequently observed in *Bacteroides* strains. However, the presence of *tetX* and *tetX1* genes in some of the strains exhibiting elevated MICs for tigecycline draws attention to the possible development and spread of resistance to this antibiotic agent among *Bacteroides* strains. The common occurrence of *ermF*, *tetX*, *tetX1* and *tetQ* genes together predicted the presence of the CTnDOT-like *Bacteroides* conjugative transposon in this collection of *Bacteroides* strains.

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1. Introduction

Since the introduction of the first tetracyclines, these antibiotics have been used widely in the treatment of bacterial infections because of their low price, oral availability and broad-spectrum antimicrobial activity. As a result of the frequent use of tetracycline, resistance to this antibiotic group has emerged during recent decades. In response to this increasing resistance, a new generation of tetracyclines, the glycylcyclines, has been developed.

Tigecycline is the first member of the glycylcycline family, a semisynthetic derivative of minocycline licensed in 2005 by the USA Food and Drug Administration (FDA). Modification of the basic structure protects tigecycline from frequent resistance mechanisms that inactivate tetracycline. The tetracycline resistance mechanisms are classified as ribosomal protection, activity of efflux pumps and enzymatic inactivation of the drug [1]. It is said that tigecycline evades the efflux pumps, which account for most of the acquired resistance against tetracycline, and binds to bacterial ribosomes that have been modified by ribosomal protection proteins, but remains vulnerable to some chromosomally encoded efflux pumps frequently present in *Pseudomonas* and *Proteus* strains [1,2].

Tigecycline displays good activity against clinically significant Gram-positive and Gram-negative bacteria, including meticillin-resistant *Staphylococcus aureus* (MRSA), penicillin-resistant *Streptococcus pneumoniae*, vancomycin-resistant *Enterococcus* and extended-spectrum β-lactamase (ESBL)-producing bacteria. All clinically important anaerobic bacteria are also highly susceptible to tigecycline [3,4]. However, in different resistance surveillance studies, *Bacteroides fragilis* group

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strains with tigecycline minimum inhibitory concentrations (MICs) >4 μg/mL have been found, which are considered tigecycline-non-susceptible according to Clinical and Laboratory Standards Institute (CLSI) breakpoints [5]. Tigecycline is recommended in the treatment of complicated intra-abdominal infections, skin and soft-tissue infections as well as infections where a polymicrobial aetiology, multiresistant pathogens or concomitant anaerobic bacteria are suspected [2,4].

The *tetQ* gene encodes a ribosomal protection protein that is responsible for most of the tetracycline resistance observed in *Bacteroides*. The *tetX* gene encodes a FAD- and NADPH-requiring oxidoreductase that inactivates tetracycline in the presence of oxygen but has been found only in strict anaerobes such as *Bacteroides* [6,7]. Two orthologues of the original *tetX* gene have been identified: *tetX1,* which is an N-terminal truncate (359 amino acids) with 66% identity to the *tetX* gene; and *tetX2*, which is 99% identical to the original gene [6]. These *tet* genes in *Bacteroides* strains are often associated with plasmids and transposons, which may contain other antibiotic resistance genes. The *tetX* gene was identified on transposons Tn*4351* and Tn*4400*, whilst *tetX1* and *tetX2* were found on a *Bacteroides* conjugative transposon, CTnDOT, together with an *ermF* gene on a specific region of it that may be a mobilisable transposon [8]. It was proposed that *tetX* may mediate glycylcycline, and hence tigecycline, resistance among *Bacteroides* spp. [2,6].

The aim of this study was to look for resistance genes that encode tetracycline and possibly tigecycline resistance in *B. fragilis* group strains with different MICs to tigecycline, including strains considered to be tigecycline-resistant.

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2. Materials and methods

2.1. Bacterial isolates and antimicrobial susceptibility testing

Thirty-five *Bacteroides* strains were selected, comprising 21 *B. fragilis*, 4 *Bacteroides ovatus*, 3 *Bacteroides thetaiotaomicron*, 2 *Parabacteroides (Bacteroides) distasonis*, 2 *Bacteroides vulgatus*, 1 *Bacteroides uniformis*, 1 *Bacteroides salyersae* and 1 *Bacteroides* sp. The selected isolates were from a strain collection compiled for a recent Europe-wide antibiotic resistance surveillance of *B. fragilis* group [5] and a national tigecycline resistance surveillance for anaerobes [9]. Selection of the strains was based on their MIC values for tigecycline, including fully susceptible strains (MIC ≤ 4 μg/mL) and strains with elevated MICs (8 μg/mL and 16 μg/mL).

The strains were stored in Cryobank vials at –70 °C until use. Pre-reduced Columbia agar (Oxoid Ltd., Basingstoke, UK) supplemented with 5% sheep blood, 10 μg/mL haemin and 1 μg/mL vitamin K1 was used for susceptibility testing. Etest gradient strips (AB BIODISK, Solna, Sweden) were applied to measure the MICs of tetracycline and tigecycline [10]. The plates were incubated for 48 h in an anaerobic chamber (Concept 400; Ruskinn Technology Ltd., Bridgend, UK). MIC values were interpreted according to CLSI breakpoints [11].

2.2. Detection of different resistance genes and calculation of their correlation with resistance levels

For the molecular genetics examinations, one colony of each strain was suspended in 100 μL of sterile distilled water and the mixture was incubated at 100 °C for 10 min and then centrifuged at 14 000 rpm for 2 min. The primers and polymerase chain

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reaction (PCR) conditions used in this study are presented in Table 1. The primers were designed by Primer3 software (http://frodo.wi.mit.edu/primer3/). The *tetX* and *tetX1* genes were detected by conventional PCR. The composition of the PCR reaction mix in this case was as follows: 1× ReadyMix™ (Sigma-Aldrich, St Louis, MO; 10 mM Tris–HCl pH 8.3, 50 mM KCl, 1.5 mM $MgCl_2$, 0.2 mM of each dNTP and 0.6 U *Taq* polymerase per reaction), 0.7 μM primer and 1/10 volume DNA extract in 20 μL final volume. The products were detected by 1.2% agarose gel electrophoresis using 0.5× TBE buffer [45 mM Tris–borate, 1 mM ethylene diamine tetra-acetic acid (EDTA), pH 8.2]. The *tetX1*, *tetQ* and *ermF* genes were detected by real-time PCR methods. The real-time PCR reactions involved 1× iQ™ RT-PCR Master-Mix (Bio-Rad, Hercules, CA), 0.7 μM primer, 1/20 volume EvaGreen® (Biotium, Hayward, CA) as a double-stranded DNA-binding fluorescent detection dye and 1/10 volume DNA extract in 20 μL final volume. *Bacteroides vulgatus* strain CLA 341 containing *tetQ* and *B. fragilis* strain BF8 containing *tetX*, *tetX1* and *ermF* (unpublished confirmed results) were used as controls.

Statistical analysis was carried out using the SPSS program package (SPSS Inc., Chicago, IL) using Pearson correlation calculations. The significance level was set to $P < 0.05$.

3. Results and discussion

Of the 35 selected *Bacteroides* strains, 12 had elevated tigecycline MICs (≥8 μg/mL) and were considered intermediate-susceptible or resistant, whilst 23 had low MICs (MIC ≤ 4 μg/mL) placing them in the susceptible range. This latter group included 8

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strains with tigecycline MICs of 4 μg/mL. The distributions of tigecycline and tetracycline MICs of the *B. fragilis* group strains are presented in Fig. 1. The resistance phenotypes of the strains for tetracycline and tigecycline are summarised in Table 2. All strains with a tetracycline MIC ≥ 8 μg/mL (intermediate or resistant) harboured the *tetQ* gene, whereas only 2 (tetracycline MIC = 4 μg/mL) of the 6 strains that were susceptible to tetracycline did so. The *tetQ* gene was present in all 12 isolates with elevated tigecycline MICs (100%), whilst *tetX* was found in 2 cases (16.7%) and *tetX1* in 9 cases (75%) (Table 3). Among the strains with a tigecycline MIC of 4 μg/mL, *tetQ* was found in 8 (100%), *tetX* in 1 (12.5%) and *tetX1* in 6 (75%). In the group of strains with tigecycline MICs between 0.064 μg/mL and 2 μg/mL, the genes were found to be present as follows: *tetQ* in 11 (73.3%); *tetX* in 2 (13.3%); and *tetX1* in 7 (46.7%). The calculated correlation values between resistance and the presence of *tetQ* and *tetX1* genes is contained in Supplementary Table 1. Presence of the *tetQ* gene correlated highly both with tetracycline and tigecycline resistance, and presence of the *tetX1* gene also correlated with tigecycline resistance although to a lesser extent. The *ermF* gene was detected in 13 (37.1%) of the 35 strains. In seven strains (six with tigecycline MICs ≥ 4 μg/mL and 1 with an MIC of 2 μg/mL) the *ermF* gene was present together with the *tetQ* and *tetX1* genes.

In the European Tigecycline Evaluation and Surveillance Trial (T.E.S.T.) study, tigecycline exhibited the lowest MICs against anaerobes and was superior to clindamycin and cefoxitin, with activity comparable with that of metronidazole or imipenem against *Bacteroides* [3]. Tigecycline resistance was also very low (1.7%) in a Europe-wide antibiotic resistance surveillance involving 824 *B. fragilis* group strains, with some differences between the different species (1.8% for *B. fragilis* and

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4.8% for *B. vulgatus*). In a Hungarian multicentre antibiotic resistance study in 2009, only 3 of 280 *Bacteroides* strains were found to be resistant (MIC ≥ 16 μg/mL), whilst 8 strains had elevated MICs (8 μg/mL) to tigecycline [9]. Using a lower resistance breakpoint for tigecycline (≥8 μg/mL), 8% of 141 *B. fragilis* group strains were found to be resistant during a recent study in Belgium [12]. It was reasonable to start to look for possible resistance genes among *Bacteroides* isolates with different MICs for tigecycline. It has been shown that the presence of *tetX*, originally found in *Bacteroides* strains, transferred to *Escherichia coli* dramatically increased MIC values of different tetracycline derivatives, including minocycline [6]. The current study revealed the presence of the *tetX* and *tetX1* genes in *Bacteroides* strains exhibiting elevated MICs for tigecycline, but a direct predictive value for tigecycline resistance could only be observed for the presence of the *tetX1* gene. In the cases of the *tetQ* and *tetX1* genes, a higher prevalence was found in strains exhibiting MICs ≥ 4 μg/mL to tigecycline (Table 3). Detection of the *tetX1* gene was included in this study despite the fact that it has been considered a pseudo-gene because we expected redox activity due to the 66% homology to the *tetX* gene. The unexpectedly high prevalence (46.7–75%) of *tetX1* is noteworthy and in our view is in contrast to it being a pseudo-gene. Presence of the *ermF* gene was also investigated because it might furnish information on the presence of genetic elements, e.g. the CTnDOT (tetracycline resistance conjugative transposon) that carries the *tetQ*, *tetX1*, *tetX2* (99% homology to *tetX*) and *ermF* genes coincidentally [8]. In this way, we found three strains that harboured the *tetQ*, *tetX* and *tetX1* genes besides the *ermF* gene. These strains could harbour CTnDOT-like conjugative transposons, and thus the prevalence of this element could be around 8.6% in this *Bacteroides* population, similar to earlier findings (10%) [13]. These studies are important from the

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perspective that the plasmids and transposons carrying these resistance genes are highly likely to promote the dissemination of these antibiotic resistance genes among bacteria. A recent study revealed that >80% of *Bacteroides* isolates currently carry conjugative transposons [13]. It is not yet clear whether the high prevalence of *tetX* and *tetX1* genes in the chromosome of *Bacteroides* strains with elevated MICs for tigecycline is a real threat, but the presence of *tetX* and *tetX1* on mobile elements emphasises the possible spread of tigecycline resistance both in *Bacteroides* and other anaerobic and aerobic strains.

Further studies are needed to transfer the tigecycline resistance from a highly resistant strain to a susceptible recipient by conjugation and to determine the possible transfer of the genes investigated in this study.

Funding

This study was partly funded by a grant from the Hungarian Scientific Research Fund (OTKA K69044), the European Union (TÁMOP-4.2.1/B-09/1/KONV-2010-0005) and the Hungarian National Office of Research and Technology (GVOP 0304).

Competing interests

None declared.

Ethical approval

Not required.

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Fig. 1. Distribution of (A) tigecycline and (B) tetracycline minimum inhibitory concentrations (MICs) among 35 selected *Bacteroides* strains.

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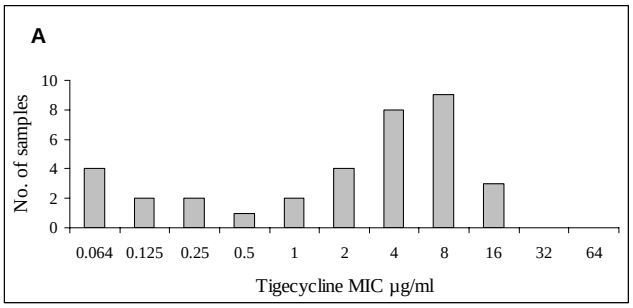

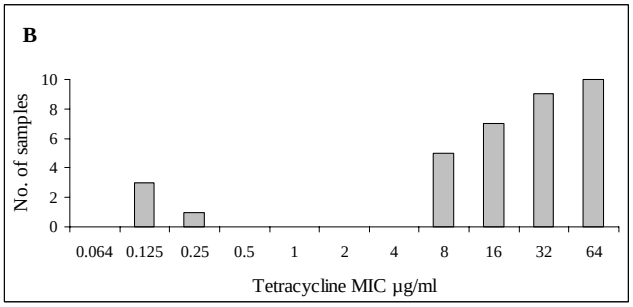

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Table 1

Primers and cycling parameters for polymerase chain reaction (PCR) experiments

Primer	Position [a]	Sequence (5'→3')	PCR conditions
tetX-1 [b]	247–267	TTAGCCTTACCAATGGGTGT	94 °C for 2 min 30 s, 94 °C for 15 s, 55 °C for 30 s, 72 °C for 30 s, 35×, 72 °C for 7 min
tetX-2 [b]	470–489	CAAATCTGCTGTTTCACTCG	
tetX1-1	106–126	TCAGGACAAGAAGCAATGAA	94 °C for 10 min, 94 °C for 10 s, 63 °C for 30 s, 72 °C for 30 s, 35×, 72 °C for 1 min 30 s, melting curve 72 °C to 94 °C
tetX1-2	236–255	TATTTCGGGGTTGTCAAACT	
tetQ-3	678–697	ATCGGTATCAATGAGTTGTT	94 °C for 10 min, 94 °C for 15 s, 50 °C for 1 min, 72 °C for 30 s, 35×, 72 °C for 1 min, melting curve 72 °C to 95 °C
tetQ-2	718–737	GACTGATTCTGGAGGAAGTA	
ermF1	113–132	TAGATATTGGGGCAGGCAAG	94 °C for 10 min, 94 °C for 15 s, 58 °C for 1 min, 72 °C for 30 s, 35×, 72 °C for 1 min 30 s, melting curve 72 °CX to 95 °C
ermF2	271–290	GGAAATTTCGGAACTGCAAA	

[a] Counted from the first nucleotide of the start codons of the respective genes.

[b] These primers could detect both *tetX* and *tetX2* genes.

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Table 2

Resistance phenotypes of *Bacteroides* strains selected for detection of resistance genes *tetQ*, *tetX, tetX1* and *ermF*

Bacteroides strains	Resistance phenotype [a]		Presence of resistance genes			
	TET	TIG	*tetQ*	*tetX*	*tetX1*	*ermF*
Tigecycline MIC 8–16 μg/mL						
B. fragilis (I 46)	R	R	+	–	+	+
B. fragilis (G 23)	R	R	+	+	+	+
B. fragilis (G 91)	R	R	+	–	+	+
B. fragilis (B26)	R	I	+	–	+	–
B. fragilis (H 2)	R	I	+	–	–	–
B. vulgatus (G 87)	R	I	+	–	+	–
B. fragilis (G 1)	R	I	+	–	+	–
B. fragilis (G 5)	R	I	+	–	+	–
B. fragilis (C 55)	R	I	+	+	+	+
B. fragilis (I 49)	R	I	+	–	–	–
B. salyersae (B 3)	R	I	+	–	–	–
B. fragilis (B 13)	R	I	+	–	+	–
Tigecycline MIC = 4 μg/mL						
B. fragilis (S 10)	R	S	+	–	+	–
B. fragilis (H 80)	R	S	+	–	+	+
B. fragilis (C 23)	R	S	+	+	+	–
B. uniformis (H 30)	R	S	+	–	–	+
B. fragilis (H 51)	R	S	+	–	–	–
B. thetaiotaomicron (C 19)	R	S	+	–	+	–
B. fragilis (F 41)	R	S	+	–	+	+
B. fragilis (F 63)	R	S	+	–	+	–
Tigecycline MIC 0.064–2 μg/mL						
B. fragilis (B 25)	R	S	+	+	+	+
B. ovatus (H 12)	R	S	+	–	–	+
B. fragilis (H 13)	R	S	+	–	+	–

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B. fragilis (H65)	R	S	+	–	+	–
B. vulgatus (H 46)	R	S	+	–	–	–
B. ovatus (H 68)	R	S	+	–	–	+
B. thetaiotaomicron (H 4)	I	S	+	–	+	–
B. ovatus (G 40)	I	S	+	–	–	+
B. ovatus (H 37)	I	S	+	–	–	–
Bacteroides sp. (H 96)	S	S	+	–	–	–
Parabacteroides (*B.*) *distasonis* (H 68)	S	S	–	+	+	+
B. fragilis (H 73)	S	S	–	–	+	–
P. (*B.*) *distasonis* (H 56)	S	S	+	–	–	+
B. thetaiotaomicron (C 47)	S	S	–	–	+	–
B. fragilis (B 15)	S	S	–	–	–	–

MIC, minimum inhibitory concentration.

[a] MIC breakpoints for tetracycline and tigecycline: susceptible (S), ≤4 μg/mL; intermediate (I), 8 μg/mL; resistant (R), ≥16 μg/mL.

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Table 3

Presence of the genes in the examined strains with different minimum inhibitory concentration (MICs) for tigecycline

Bacteroides strains with tigecycline MIC	No. (%) of strains harbouring the gene			
	tetX	*tetX1*	*tetQ*	*ermF*
≥8 μg/mL (*n* = 12)	2 (16.7)	9 (75.0)	12 (100)	4 (33.3)
4 μg/mL (*n* = 8)	1 (12.5)	6 (75.0)	8 (100)	3 (37.5)
<4 μg/mL (*n* = 15)	2 (13.3)	7 (46.7)	11 (73.3)	6 (40.0)

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