# Minimal inhibitory concentration of omadacycline and doxycycline against bacterial isolates with known tetracycline resistance determinants

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## A R T I C L E   I N F O

## A B S T R A C T

Omadacycline is an aminomethylcycline derived from the tetracycline class. The minimum inhibitory concentration of 115 Enterobacteriaceae and *Staphylococcus aureus* isolates with known tetracycline resistance determinants against omadacycline and doxycycline was determined by broth microdilution. Omadacycline is, on a weight basis, more active than doxycycline for nearly all isolates, and differences in activity correlated with organism rather than resistance mechanism.

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Antibiotic resistance is recognized as an increasing problem as therapeutic options for serious infections become more limited. The urgent need for new antibiotics is widely recognized. Tetracyclines have been used clinically for more than 50 years; however, they have lost activity against many pathogens due to resistance (Grossman, 2016). Omadacycline is an aminomethylcycline with *in vitro* activity against gram-negative bacteria and gram-positive cocci (Villano et al., 2016). It is structurally related to the tetracyclines and inhibits protein synthesis by binding to the 30S ribosomal subunit. However, it has demonstrated activity against bacteria with resistance to tetracycline by active efflux or ribosome protection mechanisms (Draper et al., 2014; Honeyman et al., 2015; Roberts, 2003). Omadacycline has IV and oral formulations and has recently been approved for acute bacterial skin and skin structure infections and community-acquired bacterial pneumonia in adults and is currently being evaluated in a phase 2 clinical study for the treatment of uncomplicated urinary tract infections (https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&varApplNo=209816; https://clinicaltrials.gov/ct2/show/NCT03425396?term=omadacycline&rank=2; last accessed November 11, 2018).

In this study, we determined the minimum inhibitory concentration (MIC) of omadacycline and doxycycline against a total of 115 Enterobacteriaceae and *Staphylococcus aureus* isolates with known tetracycline resistance determinants by broth microdilution. Doxycycline was used as a comparator as it is a common agent used to treat bacterial infections

and is susceptible to tetracycline resistance mechanisms. The isolates were selected based on results obtained by specific PCRs for tetracycline resistance determinants or on results obtained by analyzing whole genome sequences using ResFinder (Zankari et al., 2012). The isolates used are listed in Supplementary Table 1. The isolates were tested against omadacycline and doxycycline in a range of 0.06–64 mg/L using broth microdilution according to CLSI standards (Clinical and Laboratory Standards Institute (CLSI), 2015, 2016). *Escherichia coli* ATCC 25922 was used as a control for each series of isolates tested. Controls for each series were in range (data not shown). Reading of the incubated plates showed no evidence of bacterial contamination or skipped wells. None of the isolates was retested.

Differences in activity against Enterobacteriaceae isolates mainly followed species divisions rather than the mechanism of tetracycline resistance (Tables 1 and 2). MICs of omadacycline against *Escherichia coli* isolates were generally lower than against isolates of *Enterobacter*, *Klebsiella*, *Serratia*, or *Proteus* (0.25–4 and 0.5–32 mg/L, respectively). Both MSSA and MRSA showed the lowest MICs for omadacycline (0.12–2 mg/L) independent of the mechanism of resistance [*tet(K)*, *tet(M)*, or *tet(K) + tet(M)*].

These results were comparable to previously reported data from isolates that were obtained as part of large antibiotic resistance surveillance programs, but the surveillance isolates were not stratified for the presence or absence of resistance mechanisms for tetracyclines (Pfaller et al., 2017a, 2018a, b). One study differentiated tetracycline-resistant *Staphylococcus aureus*, but the MIC distribution was comparable to that reported here (Pfaller et al., 2017b). The similarity of the data in our study and the studies by Pfaller et al. (2017a, b, 2018a, b) suggests that

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**Table 1**
MIC distribution per species for omadacycline and doxycycline.

| species | N | | MIC (mg/L) | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | 0.06 | 0.12 | 0.25 | 0.5 | 1 | 2 | 4 | 8 | 16 | 32 | 64 |
| *E. aerogenes* | 2 | OMC* | | | | 1 | 1 | | | | | | |
| | | DOX | | | | | | | | | | 1 | 1 |
| *E. cloacae* complex | 15 | OMC | | | | 1 | 8 | 3 | 3 | | | | |
| | | DOX | | | | | | | 2 | 5 | 3 | 4 | 1 |
| *E. coli* | 26 | OMC | | | 1 | 1 | 7 | 15 | 2 | | | | |
| | | DOX | 1 | | | | | | 3 | 5 | 5 | 10 | 2 |
| *K. oxytoca* | 14 | OMC | | | 1 | 1 | 3 | 2 | 5 | 2 | | | |
| | | DOX | | | | | | | 2 | 2 | 4 | 4 | 2 |
| *K. pneumoniae* | 21 | OMC | | | | | 9 | 6 | 3 | 1 | 2 | | |
| | | DOX | | | | | | | | 1 | 4 | 12 | 4 |
| *Proteus* spp. | 1 | OMC | | | | | | | 1 | | | | |
| | | DOX | | | | | | | 1 | | | | |
| *S. marcescens* | 5 | OMC | | | | | 1 | 2 | 2 | | | | |
| | | DOX | | | | | | | 1 | 2 | | 1 | 1 |
| MRSA | 20 | OMC | | 2 | 4 | 9 | 4 | 1 | | | | | |
| | | DOX | | | | | | 1 | 4 | 15 | | | |
| MSSA | 10 | OMC | | 1 | 2 | 3 | 2 | 2 | | | | | |
| | | DOX | | | | 1 | | | 2 | 6 | 1 | | |

\* OMC: omadacycline; DOX: doxycycline

the presence of resistance mechanisms against tetracyclines does not affect the activity of omadacycline.

All but 6 isolates displayed lower omadacycline MICs than doxycycline MICs. In 3 cases (*E. cloacae complex* isolates 12-5557 and 10A147 and *K. pneumoniae* isolate 06A395), the MICs for both antibiotics were identical and ranged from 8 to 32 mg/L (Supplementary Table 1). In 3 cases, the MICs for omadacycline were 2–4-fold higher than for doxycycline. The MICs for *E. coli* isolate MA-13773 and MSSA isolate 05A039 were at the lower end of the MIC distribution for both antibiotics with MIC values of 0.25 and 0.5 mg/L for omadacycline *versus* 0.06 and 0.25 mg/L for doxycycline, respectively. *Proteus* spp. isolate 8247 had higher MICs for these antibiotics of 8 and 2 mg/L, respectively (Supplementary Table 1). Omadacycline was generally more potent than doxycycline in our study. Differences in activity followed species differences independent of the tetracycline resistance determinant.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diagmicrobio.2018.11.010.

**Table 2**
MIC distribution per resistance determinant for omadacycline and doxycycline.

| Gene | N | | MIC (mg/L) | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | 0.06 | 0.12 | 0.25 | 0.5 | 1 | 2 | 4 | 8 | 16 | 32 | 64 |
| **Enterobacteriaceae** | | | | | | | | | | | | | |
| *tet(A)* | 31 | OMC | | | 1 | | 1 | 8 | 9 | 6 | 5 | 1 | |
| | | DOX | 1 | | | | | | 4 | 8 | 9 | 8 | 1 |
| *tet(B)* | 26 | OMC | | | | 2 | 6 | 8 | 4 | 4 | 2 | | |
| | | DOX | | | | | | | 1 | 4 | 4 | 12 | 5 |
| *tet(D)* | 19 | OMC | | | | | 1 | 12 | 4 | 1 | | | 1 |
| | | DOX | | | | | | | | 3 | 12 | 4 | |
| Other *tet* genes[a] | 8 | OMC | | | | | 1 | 2 | 3 | 1 | 1 | | |
| | | DOX | | | | | | 1 | 1 | 3 | 1 | 1 | 1 |
| **S. aureus** | | | | | | | | | | | | | |
| *tet(K)* | 10 | OMC | | | 5 | 4 | 1 | | | | | | |
| | | DOX | | 1 | | | | 1 | 2 | 6 | | | |
| *tet(M)* | 10 | OMC | | 2 | | 3 | 2 | 3 | | | | | |
| | | DOX | | | | | | | 1 | 8 | 1 | | |
| *tet(K) + tet(M)* | 10 | OMC | 1 | 1 | 5 | 3 | | | | | | | |
| | | DOX | | | | | | | 3 | 7 | | | |

Results for 1 *E. cloacae* complex carrying *tet(C)*, 1 *Proteus* spp. carrying *tet(J)*, 3 *S. marcescens* carrying *tet(41)*, 1 *E. coli* carrying *tet(A)* + *tet(B)*, 1 *K. oxytoca* carrying *tet(B)* + *tet(C)*, and 1 *K. oxytoca* carrying *tet(B)* + *tet(D)*.

## Conflict of interest

None to declare.

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