

# Amiodarone and tetracyclines has synergistic antibacterial effect

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## Introduction

Patients treated in intensive care units usually require the intravenous co-administration of drugs with different mechanism of action for acute and chronic illness, infection, pain relief, and sedation. Non-antibiotics may have synergistic antimicrobial effect of an antibiotic in vitro (1). The antifungal synergism of amiodarone and an azole compound for *Candida albicans* is already known (2). In this study we investigated the impact of amiodarone on the bactericidal effect of antibiotics.

## Methods

Amiodarone infusion was contaminated with low colony forming units (cfu) of standard bacterial strains (*Staphylococcus aureus* ATCC 25923, *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 27853) separately and bacterial count was checked at intervals. Minimal inhibitory concentration (MIC) of the drugs were determined (according to CLSI) and compared with serum concentration. Checkerboard method (Figure 1) was used for investigation of combined effect of amiodarone and antibiotics (see Table 1) with different mechanism of action. We determined the fractional inhibitory concentration index what is the predictor of synergism.

$$\sum FIC = FIC_A + FIC_B = \frac{MIC_{A,komb}}{MIC_A} + \frac{MIC_{B,komb}}{MIC_B}$$

A: antibiotic

B: non-antibiotic

$FIC \leq 0,5$  - synergistic

$0,5 < FIC < 4$  - non synergistic

$4 \leq FIC$  - antagonistic

Table 1 Antibiotics and non-antibiotic

Amoxicillin+clavulanic acid (Augmentin®

GlaxoSmithKline Beecham)

Cefotaxime (Cloforan® Sanofi-Aventis)

Imipenem+cilastin (Tienam® MDS)

Gentamicin (Chinoïn)

Amikacin (Amikin® Bristol-Myers Squibb)

Ciprofloxacin (Ciprobay® Bayer Schering Pharma AG)

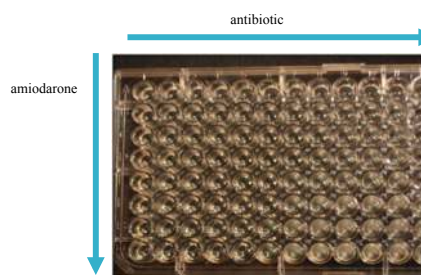
Oxytetracyclin (Békéscsaba Gyógyszerkíszerelő labor)

Chloramphenicol (University of Pécs, Pharmacy 345/03)

Amiodaron (Cordarone® Sanofi-Aventis)-150mg/3 ml

Diluted in 250ml of 5% glucose infusion

Figure 1. Checkerboard method



## Results

$5 \times 10^3$  cfu bacteria did not survive in amiodarone infusion after 15 minutes. MIC levels of both drugs are higher than the serum concentration of drugs (2,8 microg/ml). There were synergistic antimicrobial effects of combined amiodarone and oxytetracycline against standard bacterial strains. (Table 2.-3.)

Table 2. Amiodarone MIC level

Strains	Amiodarone MIC
<i>S. aureus</i>	200 microg/ml
<i>E. coli</i>	300 microg/ml
<i>P. aeruginosa</i>	300 microg/ml

Table 3. Fractional inhibitory concentration indexes

Amiodarone+	amoxicillin	cefotaxime	imipenem	oxytetracyclin	gentamicin	ciprofloxacin
<i>S. aureus</i>	0.5-1.09	0,06*-0,207*	0,144*- 0.54	0,046*-0,07*	1,256	0,167*-0.635
<i>E. coli</i>	0,25*-1.19	1,65 - 3.16	0,14* - 0.54	0,07* - 0,245*	1,258	0,31* - 1.01
<i>P. aeruginosa</i>	NA	0,215* - 0,78	0,043*-0,14*	0,069*-0,245*	0.636	0,312* - 1,249

$FIC \leq 0,5$  synergistic

## Conclusions

Non-antibiotics might have antimicrobial synergistic effect with some antibiotics, thus they may contribute to the killing of pathogens when they are co-administrated. Further research is required whether there is any *in vivo* synergistic effect resemble for the above *in vitro* results.

References: (1) Nat Chem Biol 2011; 7: 348. (2) J Med Microbiol 2008; 57:457.