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Erythromycin-induced insensitivity of coagulase-negative staphylococci to telithromycin

Erytromycyna jako induktor oporności na telitromycynę u gronkowców koagulazo-ujemnych

INTRODUCTION

Coagulase-negative staphylococci (CoNS) belong to natural microflora of skin and mucous membrane of the upper respiratory tract. The isolates of natural microflora are useful in predicting drug resistant patterns of pathogenic strains (*e.g. Staphylococcus aureus*) in a given population as a result of transferring the genes between the species [10]. Telithromycin represents new group of antibiotics – ketolides, belonging to the same family as MLSB (macrolides, lincosamides, streptogramins B antibiotics). Ketolides are inhibitors of protein synthesis as a result of binding with subunit 23S rRNA (domain II and V) [5].

The aim of this study was to determine minimal inhibitory concentration (MIC) of telithromycin for nasopharyngeal, erythromycin-resistant CoNS isolates both in the absence and in the presence of erythromycin in the medium.

MATERIAL AND METHODS

Bacterial strains. The collection of 95 erythromycin-resistant CoNS isolates from throat or nasal specimens of patients with non-small cell lung cancer undergoing pulmonary resection were included in the present study. Among them 38, isolates expressed inducible MLSB resistance, 16 strains – constitutive MLSB resistance and 41 strains – MSB resistance. The routine microbiological tests were used for isolation and identification of staphylococci.

Determination of MIC of telithromycin. The double dilution micromethod was used for evaluation of MIC of telithromycin for CoNS strains, according to the guidelines of Clinical and Laboratory Standards Institute (CLSI) and French Society of Microbiology [2,7]. Susceptibility of the strains to telithromycin was determined basing on the following breakpoints: $\leq$ 0.5 mg/l –

susceptible, > 2 mg/l – resistant [2]. The standard Mueller-Hinton medium and also the same medium containing erythromycin (5 mg/l) were used.

RESULTS

Among the assayed nasopharyngeal CoNS isolates resistant to erythromycin, 53/95 (55.8%) strains were susceptible to telithromycin with MIC range of 0.015–0.5 mg/l, including 16/38 (42.1%) strains with inducible MLSB resistance, 5/16 (31.2%) isolates with constitutive MLSB resistance and 32/41 (78%) strains with MSB resistance. The remaining 42/95 (44.2%) isolates were resistant to telithromycin with MIC's > 16 mg/l. Among the susceptible strains, the MICs of telithromycin in the presence of erythromycin increased in case of 50/53 (94.3%) isolates reaching values between 0.5 to >16 mg/l, irrespective of the MLSB phenotype; in case of 35/53 (66%) isolates MIC reached values above 2 mg/l, typical telithromycin-resistant strains (Figure 1).

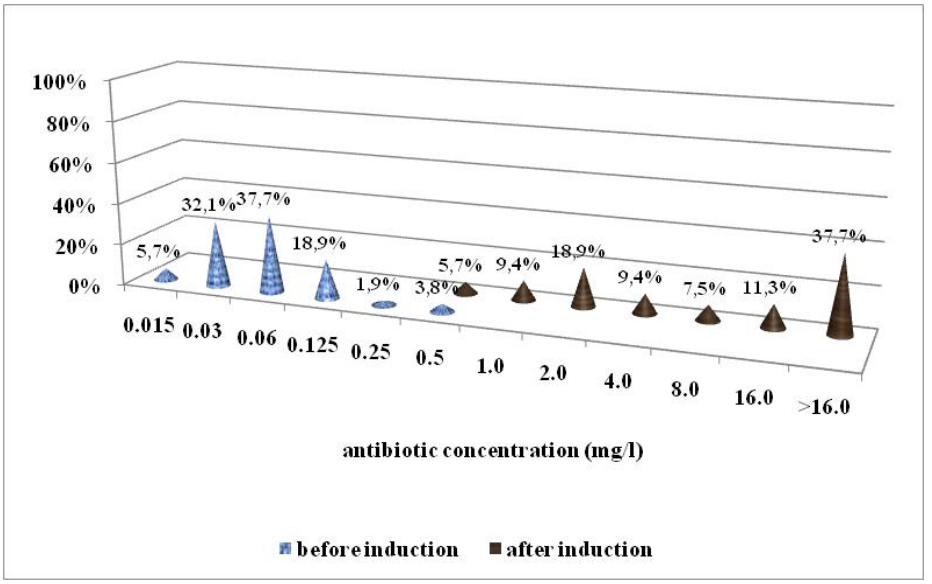

Fig. 1. The minimal inhibitory concentration values of telithromycin in the presence of erythromycin (5 mg/l) of coagulase-negative staphylococci susceptible to telithromycin (n = 53)

DISCUSSION

Nowadays, the major problem in the treatment of infectious diseases is rapidly increasing resistance of bacterial pathogens to the available antibiotics, including cross-resistance, where one antibiotic induces the resistance to another antimicrobial agent. An example of this phenomenon is the MLS_B resistance among *Staphylococcus* spp. or *Streptococcus* spp. Erythromycin is a known

good inducer of the expression of *erm* genes in strains with inducible MLS_B resistance, leading to the production of methyltranferase responsible modification of the antibiotic target in the bacterial ribosome [4].

The data presented in this paper showed the possibility of erythromycin induction of the resistance to telithromycin among erythromycin-resistant CoNS isolates with various phenotypes of MLS_B resistance. The mechanism of this phenomenon has not been understood yet. Literature data [1,3,8,9] suggest that the *msrA* and *msrC* genes, responsible for efflux of 14- and 15-membered macrolides, may confer inducible resistance to telithromycin. Also, the data of Novotná et al. [6] showed a strong correlation between the presence of the *msrA* gene and inducible resistant to telithromycin among CoNS isolates.

CONCLUSIONS

It is not recommended to test routinely the clinical isolates of CoNS for inducible telithromycin resistance. The clinical significance of this phenomenon has not been reported yet. However, it is very important to study this mechanism of resistance, especially before the introduction of the new ketolide as cethromycin.

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SUMMARY

Telithromycin represents a new group of antibiotics, called ketolides, belonging to the same family as MLS_B (macrolide, lincosamide, streptogramin B) antibiotics. The aim of this study was to determine minimal inhibitory concentration (MIC) of telithromycin for nasopharyngeal, erythromycin-resistant isolates of coagulase-negative staphylococci both in the absence and presence of erythromycin in the medium. The increased MIC values for telithromycin were noted in the presence of erythromycin, suggesting the possibility of erythromycin-mediated induction of resistance to telithromycin in this group of strains. The mechanism and clinical significance of this phenomenon has not been known yet.

Key words: coagulase-negative staphylococci, telithromycin, erythromycin, inducible resistance

STRESZCZENIE

Telitromycyna należy do nowej grupy antybiotyków, jakimi są ketolidy; należą one do tej samej rodziny co antybiotyki klasy MLS_B (makrolidy, linkozamidy, streptograminy B). Celem pracy była ocena wartości MIC telitromycyny dla opornych na erytromycynę gronkowców koagulazo-ujemnych w warunkach standardowych oraz w obecności erytromycyny w podłożu. Wyniki uzyskane w niniejszej pracy wskazują na możliwość indukcji oporności na telitromycynę w obecności erytromycyny w tej grupie szczepów. Znaczenie kliniczne oraz mechanizm tej indukcyjnej oporności nie są jeszcze do końca poznane.

Słowa kluczowe: gronkowce koagulazo-ujemne, telitromycyna, erytromycyna, oporność indukcyjna