Efflux pump inhibitors and NMP Diatabs

Introduction

The accelerated evolution of antibiotic resistance to important human pathogens and the scarcity of new antiinfective drug families under development, makes that other ways are being tried.
Efflux is a general mechanism responsible for bacterial resistance to antibiotics. This active drug transport is involved in low intrinsic susceptibility, cross resistance to chemically unrelated classes of molecules and selection/acquisition of additional mechanisms of resistance.
As a consequence, inhibition of bacterial efflux mechanisms appears to be promising in order to a) increase the intracellular concentration of antibiotics, that are expelled by efflux pumps b) restore the drug susceptibility of resistant clinical strains and c)reduce the capability for acquired additional resistance(1).
The resultant efflux pump inhibitor/antibiotic combination drug should exhibit increased potency, enhanced spectrum of activity and reduced propensity for acquired resistance (2)

Enterobacteriaceae

Kim et al (3) found that Shigella flexneri isolated in Korea and resistant to fluoroquinolones, showed an increased susceptibility
to ciprofloxacin, norfloxacin and ofloxacin in the presence of an efflux pump inhibitor (CCCP).
Freyre et al (4) studied the effect of an inhibitor of efflux pumps (PABN)on the MICs to different fluoroquinolones in clinical isolates of E.coli. Strains resistant to the fluoroquinolones showed an increased reduction of the MICs for levofloxacin and moxifloxacin.
Tran QT et al (5) studied the effect of the efflux pump inhibitor PABN on the resistance of Enterobacter aerogenes and K. pneumoniae.
Efflux was involved in resistance (chloramphenicol, sparfloxacin) in E. aerogenes isolates more frequently than in K. pneumoniae.
Kern WV et al (6) studied the efflux pump inhibitor 1-(1-naphthylmethyl)-piperazine (NMP)on clinical isolates of E. coli.
NMP was moderate active in reversing multidrug resistance in clinical isolates of E. coli and can partially restore fluoroquinolone susceptibility through inhibition of efflux pumps.
Schumacher A et al (7) studied the effect of NMP on drug susceptibility of Enterobacteriacea (other than E.coli).NMP has shown to reverse multidrug resistance in E. coli overexpressing RND type efflux pumps. On other Enterobacteriaceae, NMP consistently reduced the MIC of linezolid in C. freundii, Enterobacter aerogenes and K. pneumoniae clinical isolates. Significant effects were also seen for levofloxacin, tetracycline and chloramphenicol in E aerogenes, and for levofloxacin and tetracycline for K. pneumoniae. Effect of NMP was more likely in isolates with decreased susceptibility to fluoroquinolones.

Non-fermenters and Vibrio

Bina XR et al (8) studied the effect of NMP on antimicrobial susceptibility and virulence factor production in Vibrio cholera.
NMP potentiated antimicrobial compounds that were substrates for the V. cholerae RND efflux systems. NMP inhibited the production of virulence factors cholera toxin and the toxin coregulated pilus.
Bean D et al (9) found that A. baumannii belonging to the multidrug resistant OXA-23 clone1 appeared to decrease in susceptibility to tigecycline in the presence of NMP. The converse was seen when NMP was combined with doxycycline, tetracycline or minocycline. The synergy seen between NMP and the tetracyclines must be due to NMP effect against the AdeABC resistance-nodulation division efflux pump.
Vila J et al (10) give a review of porins, efflux pumps and multidrug resistance in Acinetobacter baumannii. The efflux pump AdeABC of the family RND affects the following antimicrobials: aminoglycosides, betalactams, chloramphenicol, erythromycin, tetracyclines and reduced susceptibility to fluoroquinolones.
Lomovskaya O et al (11) identify and characterize the inhibitors of multidrug resistance efflux pumps in P. aeruginosa. They conclude that inhibition of efflux pumps in P aeruginosa may significantly improve the clinical performance of fluoroquinolones. It would suppress the emergence of S. aureus and pneumococci mutants resistant to ciprofloxacin.

NMP Diatabs

Rosco has developed a test (NMP Diatabs) for detecting efflux pumps, particularly of the RND family.
The test is performed on Mueller Hinton Agar using Mc farland 0.5 inoculum and the NMP Diatabs (9 mm) is placed near the corresponding Neo-sensitabs that should be tested for synergy.
The distance between NMP Diatabs and Neo-sensitabs, will depend on the size of the inhibition zone of the corresponding Neo-sensitabs with the particular bacteria. If the zone is <= 20 mm, the NMP tablet should be placed 6-8 mm apart (edge to edge). If the zone is >=30 mm the distance should be 10-12 mm apart.
Synergy (enlargement of the zone of inhibition, keyhole zone or phantom zone) indicates the presence of an Efflux Pump, probably of the RND family.

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