Study on Post-Antimicrobial effect (PAE) of certain Antimicrobial Agents on certain Bacterial Isolates

The impact of using a combination therapy on improving the pharmacodynamic parameters (killing activity and postantibiotic effect [PAE]) of certain antimicrobials (aminoglycosides {amikacin and gentamicin}, quinolones {ofloxacin and ciprofloxacin} and β-lactams{meropenem, imipenem, cefuroxime, cefotaxime, cefoperazone, ceftazidime and cefepime) against common opportunistic pathogen" *Enterobacteriaceae*" was the focus of this study. Firstly, screening for a number of different members of *Enterobacteriaceae* sensitive to the previously mentioned antimicrobials was done by identifying and performing disk-diffusion susceptibility testing over a sample of 94 MacConkey isolates, most of them were provided sensitive toward many classes of antimicrobial agents. A nine different enterobacterial isolates namely; *E.coli* strain 19, *Klebsiella pneumonia* strain 63, *Klebsiella oxytoca* strain 68a, *Enterobacter cloacae* strain 35a, *Citrobacter koseri* strain 4b, *Citrobacter freundii* strain 52, *Proteus mirabilis* strain 5b, *Proteus vulgaris* strain 50b and *Providencia rettgeri* 14a were sensitive to antimicrobials of the study and selected the following study steps. Secondly, the minimum inhibitory concentrations {MIC} were determined for the antimicrobials of the study against the 9 selected representative strains via agar dilution method. It was noticed that meropenem has the lowest MIC values while cefuroxime has the highest MIC values against the selected bacteria. After that, the bactericidal activity and the killing rates were investigated for individual antimicrobials and combinations of them against the selected enterobacteria via killing curve methodology. It

was found that all antimicrobials used have significant bactericidal activity and it was found also that quinolones; ciprofloxacin and ofloxacin induced the highest killing rate at different multiples of their MICs followed by aminoglycosides; amikacin and gentamicin then carbapenem-β-lactams; imipenem and meropenem and it was noticed that all the previous antimicrobials induced concentration dependent killing activity. Finally, cephalosporine-β-lactams induced the least powerful and only time dependent killing against the various selected bacteria. The killing rates of the combinations of aminoglycosides used (at 2xMIC) with various β-lactams of the study (at 10xMIC) also, the combinations of aminoglycosides (at 2xMIC) with quinolones (at 2xMIC) were investigated via killing curve method against the nine bacterial strains and compared to the killing rate induced by individual agents. The resulted data and figures showed clear synergism between aminoglycosides and β-lactams of the study. While showing indifferent killing activity with aminoglycosides-quinolones combinations from that induced by individual antimicrobial agents against all selected bacteria.

The other major concern was the studying of PAE of individual antimicrobials and the combinations, and the study showed that quinolones, aminoglycosides and carbapenem β-lactams induced significant PAEs while cephalosporins-β-lactams induced non-significant or even negative PAEs. We also studied the combinations of aminoglycosides; amikacin and gentamicin (at 2xMIC) with various β-lactams (at 10xMIC) and with quinolones used (at 2xMIC) against the previously selected 9 *Enterobacteriaceae*. It was observed that combinations of aminoglycosides with β-lactams showed synergistic improvement for PAE-periods, thus, permitting less frequent administration of both agents during the practical situations in therapy. While combinations of aminoglycosides with

quinolones did not enhance PAE to reach to synergistic level (not even be additive) and consequently considered indifferent with respect to PAE. So the combinations of aminoglycosides with quinolones have no beneficial impact on dosing frequency of them.

Also the impact of the utilization of an antineoplastic agent 5-Flurouracil " 5-FU" [at 50 μg/ml; corresponding to the maximum achievable plasma concentration] on PAE duration of antimicrobials (at the previous multiple of MIC) against *Proteus mirabilis* and *Providencia rettgeri* was studied. The MICs of 5-FU against the 9 *Enterobacteriaceae* revealed that the MICs of 5-FU against *Proteus mirabilis* and *Providencia rettgeri* were below the maximum achievable plasma concentration (50 μg/ml) while, its MICs against the other selected strains much higher than 50 μg/ml. The results showed that the PAEs of 5-FU at 50 μg/ml toward *Proteus mirabilis* and *Providencia rettgeri* were high being 2.5 and 2 hours, respectively. It was observed that a synergistic enhancement of PAE of ofloxacin and ciprofloxacin at 2xMIC and of β-lactams; meropenem, cefepime, cefotaxime, ceftazidime and cefoperazone at 10xMIC in presence of 5-FU occurred. While, aminoglycosides; amikacin and gentamicin at 2xMIC induced PAE in presence of 5-FU indifferent from that induced by the antimicrobial alone, against *Proteus mirabilis* and *Providencia rettgeri*. Consequently, the patients who take 5-FU as anticancer therapy could lower the dosing frequency of quinolones and β-lactams used for treatment of enterobacterial infection, especially, if bacteria inhibited with 5-FU-MIC below the maximum achievable plasma concentration of 5-FU.