ALTERATIONS OF OUTER MEMBRANE PROTEINS IN MULTIPLE-DRUG RESISTANCE MUTANTS OF PROTEUS MIRABILIS SELECTED BY LEVOFLOXACIN

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ABSTRACT

A total of 6 spontaneous levofloxacin-resistant mutants were isolated from Proteus mirabilis clinical isolate on agar plates containing levofloxacin (6 times MICs). Five of these mutants (PM1-PM3, PM5, and PM6) are characterized by cross-resistance to other fluoroquinolones (norfloxacin, and ofloxacin), β-lactam antibiotics (cephalothin, cefamandole, cefoperazone, and cefotaxime), aztreonam, and chloramphenicol. While the sixth mutant (PM4) is characterized by selective resistance to the tested fluoroquinolones. The outer membrane proteins (OMPs) analysis showed a significant reduction (in PM3 and PM5 mutants) or disappearance (in PM1 and PM2 mutants) of 39 KDa OMP and expression of 48 and 52 KDa OMPs in PM6 mutant as compared to the parent isolate. In case of mutant PM4, no significant change in the OMP profile was observed. The five multiple-drug resistant mutants (PM1-PM3, PM5, and PM6) had about 2.7- to 4.4-time lower rate of norfloxacin uptake than that of the parent isolate, while no significant change in norfloxacin uptake was observed in case of PM4 mutant. Addition of 0.25 mM carbonyl cyanide m-chlorophenylhydrazone increased the norfloxacin uptake by only PM6 mutant, while no change was observed in case of the other mutants. The results of β-lactamase induction and DNA gyrase assay showed no difference between the selected mutants and their parent, with exception for PM4 mutant in which a significant decrease in the DNA gyrase sensitivity to levofloxacin was observed. These data suggest that reduction or disappearance of 39 KDa and expression of 48 and 52 KDa OMPs in P. mirabilis isolate is associated with cross-resistance to fluoroquinolones, β-lactam antibiotics, aztreonam, and chloramphenicol.