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Research Article

Contribution of AcrAB efflux pump to ciprofloxacin resistance in Klebsiella pneumoniae isolated from burn patients

Beitrag der AcrAB-Effluxpumpe zur Ciprofloxacin-Resistenz von Klebsiella pneumoniae, isoliert von Patienten mit Verbrennungen

Abstract

Resistance to fluoroquinolones has been recently increased among bacterial strains isolated from outpatients. Multidrug-resistant *K. pneumoniae* is one of the major organisms isolated from burn patients and the AcrAB efflux pump is the principal pump contributing to the intrinsic resistance in *K. pneumoniae* against multiple antimicrobial agents including ciprofloxacin and other fluoroquinolones.

Fifty-two *K. pneumoniae* isolated from burn patients in Shahid Motahari hospital and confirmed by conventional biochemical tests. Antimicrobial susceptibility testing was done according to CLSI 2011 guidelines, to determine the antimicrobial resistance pattern of isolates. *Acr*A gene was detected among ciprofloxacin-resistant isolates by PCR assay. MICs to ciprofloxacin were measured with and without carbonyl cyanide 3-chlorophenylhydrazone (CCCP). Forty out of the 52 *K. pneumoniae* isolated from burn patients in Shahid Motahari hospital were resistant to ciprofloxacin according to breakpoint of CLSI guideline. PCR assay for *acr*A gene demonstrated that all ciprofloxacin-resistant isolates harbored *acr*A gene coding the membrane fusion protein AcrA and is a part of AcrAB efflux system. Among these isolates, 19 strains (47.5%) showed 2 to 32 fold reduction in MICs after using CCCP as an efflux pump inhibitor. The other 21 strains (52.5%) showed no disparity in MICs before and after using CCCP. In conclusion, the AcrAB efflux system is one of the principal mechanisms contribute in ciprofloxacin resistance among *K. pneumoniae* isolates but there are some other mechanisms interfere with ciprofloxacin resistance such as mutation in target proteins of DNA gyrase of topoisomerase IV enzymes.

Keywords: ciprofloxacin resistance, efflux system, Klebsiella pneumoniae

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Zusammenfassung

Die Resistenz gegen Fluorchinolone ist in letzter Zeit bei von ambulanten Patienten isolierten Bakterienstämmen angestiegen. Multiresistente *K. pneumoniae* gehören zu den wichtigsten von Patienten mit Verbrennungen isolierten Mikroorganismen und die AcrAB-Effluxpumpe ist die hauptsächliche Effluxpumpe, die für die intrinsische Resistenz von *K. pneumoniae* gegen mehrere antimikrobielle Wirkstoffe einschließlich Ciprofloxacin und andere Fluorchinolone verantwortlich ist.

Im Shahid Motahari Krankenhaus wurden 52 *K. pneumoniae*-Isolate von Patienten mit Verbrennungen durch konventionelle biochemische Tests bestätigt. Die antimikrobielle Empfindlichkeit der Isolate wurde gemäß der CLSI Guideline (2011) getestet. Bei Isolaten mit Ciprofloxacinresistenz wurde das *acr*A-Gen mit einem PCR-Assay bestimmt. Die MHK gegen Ciprofloxacin wurden mit und ohne den Entkoppler Carbonylcyanid-3-chlorphenylhydrazon (CCCP) bestimmt.

Gemäß dem Breakpoint der CLSI Guideline waren alle 52 *K. pneumoniae*-Isolate der Verbrennungspatienten des Shahid Motahari Hospitals resistent gegen Ciprofloxacin. Der PCR-Assay für das *acr*A-Gen zeigte, dass alle Ciprofloxacin-resistenten Isolate das *acr*A-Gen enthielten, das das Membranfusionsprotein AcrA codiert und ein Teil des AcrAB-Effluxsystems ist. Nach Zugabe von CCCP als Inhibitor der Effluxpumpe zeigten 19 Stämme (47,5%) eine 2–32-fache Reduktion der MHK. Die anderen 21 Stämme (52,5%) zeigten keine Unterschiede in der MHK vor und nach Zugabe von CCCP.
Zusammenfassend ist das AcrAB-Effluxsystem einer der wichtigsten Mechanismen für die Ciprofloxacinresistenz gegen *K. pneumoniae*, aber es gibt weitere Mechanismen wie die Mutation der Targetproteine der DNA-Gyrase des Topoisomerase-IV-Enzyms.

Schlüsselwörter: Ciprofloxacinresistenz, Effluxsystem, Klebsiella pneumoniae

1 Background

Klebsiella pneumoniae is one of the major agents in nosocomial infections that include infection of the urinary tract, the respiratory system, wounds and also the blood stream [1], [2]. According to the data by the World Health Organization (WHO) a high amount of people die of pneumonia annually all over the world (http://www.who.int/whr/2004/annex/en/index.html). Appearance of multidrug-resistant species of *K. pneumoniae* has increased recently in the world [3]. *Klebsiella* spp. have been found to harbor plasmids which is responsible for resistance to β-lactams especially extended-spectrum cephalosporins and also carbapenams [4]. All these properties lead to difficult treatment of patients infected with multidrug resistant strains (MDR) of *K. pneumoniae* by using antimicrobial agents and the treatment will implicate a shift in strategies of fluoroquinolone usage. Resistance to fluoroquinolones has recently increased among bacterial strains isolated from outpatients [5]. Fluoroquinolones resistantance mainly occurred through specific mutations in DNA gyrase and topoisomerase IV and over-expression of AcrAB multidrug efflux system. Both resistance mechanisms have been demonstrated in different organisms such as *Escherichia coli* [6], *Pseudomonas aeruginosa* [7], *Staphylococcus aureus* [8], *Streptococcus pneumoniae* [9] and *Klebsiella pneumoniae* [3]. Efflux pumps are transport proteins which are responsible for intrinsic or acquired resistance to different antibiotics based on chromosomal or plasmids sources of efflux genes, respectively. These proteins are found in both Gram-negative and -positive bacteria and extrude toxic substrates including antibiotics within cells into the external environment [10]. AcrAB efflux pumps can change the permeability of the bacterial membrane by antibiotics extrusion to external environment thus the intracellular concentration of antibiotic reduces and the resistance to antibiotic will occur [11]. Five major families of efflux pumps have been found in prokaryotic kingdom which AcrAB-TolC efflux pump has been classified as RND (resistance-nodulation-division) family. RND efflux pumps are one of the most important multidrug resistance efflux pumps and play a major role in multidrug resistance in bacteria by excreting antibiotics from different classes. CCCP is an uncoupler of oxidative phosphorylation, which disrupts the proton gradient of the membranes, required for activity of RND-type pumps including AcrAB thus AcrAB efflux pump have no inactivity in the present of CCCP [11]. Over expression of genes belong to multidrug efflux pumps result in increasing resistance of bacteria against multiple drugs [12]. AcrAB has been recognized as a principal pump contributing to the intrinsic resistance in *E. coli* against multiple antimicrobial agents [13], [14]. Over expression of AcrAB was detected in other MDR strains of *Enterobacteriaceae* family such as *Salmonella enterica*, *Enterobacter aerogenes*, *E. coli*, *Proteus mirabilis*, and *K. pneumoniae* [3], [13], [15], [16], [17]. AcrAB efflux pump can provide resistance against quinolones, chloramphenicol, tetracycline, trimethoprim, and β-lactams [18], [19], [20], [21], [22].
The aim of this study was to evaluate the presence of AcrAB efflux system by PCR assay and to demonstrate the role of active AcrAB efflux pump in resistance to ciprofloxacin among *K. pneumoniae* isolated from burn patients in Shahid Motahari hospital, Tehran (referral center of burn patients).

2 Materials and methods

2.1 Isolation of bacterial strains

Fifty-two strains of *Klebsiella pneumoniae* were isolated during 6 months from hospitalized burn patients in Shahid Motahari Hospital, Tehran. Clinical conventional biochemical tests including triple sugar iron (TSI), urea, indole, ornithine decarboxylase, motility, growth in KCN medium, production of H_2S , phenylalanine deaminase, simmons citrate test and etc. were performed for final identification of isolates.

2.2 Antimicrobial susceptibility testing

Antimicrobial susceptibility testing was performed by disk diffusion method according to Clinical and Laboratory Standards Institute (CLSI) guidelines 2011 [23]. Each *Klebsiella pneumoniae* isolate was tested for susceptibility to 15 different antimicrobial agents including Imipenem (IMI), Ceftazidime (CAZ), Cefalosporine (CEF), Ticarcillin (TC), Aztreonam (AT), Tobramycin (TOB), Gentamicin (GN), Colistin (CO), Cefotaxime (CTX), Ciprofloxacin (CIP), Amikacin (AK), Cotrimoxazole (SXT), Piperacillin-tazobactam (PTZ), Piperacillin (PIP) and Tetracycline (TET) (MAST, Merseyside, U.K). *E. coli* ATCC 25922 was used as quality control for all antimicrobial susceptibility tests. According to CLSI guideline 2011, *K. pneumoniae* strain with zone of inhibition ≤15 mm for ciprofloxacin disk should be reported as ciprofloxacin-resistant strains. All the ciprofloxacin-resistant isolates subjected to evaluate MIC of ciprofloxacin by agar dilution technique according to CLSI guideline [23].

2.3 Presence of AcrAB efflux pump among Ciprofiloxacin-resistant isolates

Total genomic DNA was extracted by boiling method and used as a template for PCR reaction. Specific primers for *Acr*A gene (*Acr*A-F, 5´-ATGAACAAAAACAGAGG-3´ and *Acr*A-R, 5´-TTTCAACGGCAGTTTTCG-3´) was used to evaluate the presence of AcrAB efflux pump. PCR reaction was performed in mixture, containing 1 × PCR buffer, 0.4mmol l^{-1}dNTP, 0.7 mmol l^{-1} $Mgcl_2$, 10 pmol l^{-1} of each primers, 1 U Taq DNA polymerase, 5 µl DNA template and distilled water up to final mixture volume of 25 µl and was done as follow: initial denaturation step at 94 °C for 5 min followed by 30 cycles consisting of denaturation (94 °C for 1 min), annealing (52 °C for 1 min) and extension (72 °C for 1 min), followed by a final extension step at 72 °C for 5 min. PCR products were analyzed by electrophoresis in a 1% vw^{-1}agarose gel. One of the PCR products was purified using QIAquick Gel Extraction Kit (Qiagen,Valencia, CA) and direct sequencing was done using ABI 3730X capillary sequencer (Macrogen, Seoul, Korea).

2.4 Inhibition of efflux pump activity by CCCP

The functionality of efflux pump was assessed by comparison the MICs to ciprofloxacin among resistant isolates before and after treatment with CCCP as an efflux pump inhibitor. CCCP can disrupt the proton gradient of the membrane and inhibit the activation of RND family efflux pumps including AcrAB pump [11]. Addition of CCCP in Mueller-Hinton agar plates leads to an increase in intracellular concentration of antibiotics and consequently, reduce the MIC value in isolates carrying active efflux pumps. MIC to ciprofloxacin among 40 ciprofloxacin-resistant isolates was determined in Mueller-Hinton Agar plates containing different concentration of ciprofloxacin from 0.5 to 256 µg ml^{-1} according to CLSI guideline, 2011 [23], *E. coli* ATCC 25922 was used as control. To compare the AcrAB efflux pump activity in presence inhibitor, CCCP was added to each Mueller-Hinton agar plates containing 0.5–256 µg ml^{-1} of ciprofloxacin at final concentration of 25 µg ml^{-1}. Plates containing CCCP but no ciprofloxacin were used as control.

3 Results

3.1 Bacterial isolates and antibiotic resistance pattern

Forty isolates out of 52 (77%) were resistant to ciprofloxacin and all of the ciprofloxacin-resistant isolates were resistant to tetracycline. Thirty-eight (95%) of ciprofloxacin-resistant isolates were resistant to tetracycline, imipenem, ceftazidime, cefalosporine, ticarcillin, aztreonam, tobramycin and gentamicin since they showed resistance to three different groups of antibiotics were reported as multidrug resistant (MDR) strains. The two remain strains were resistant to mentioned antibiotics except imipenem.

3.2 Molecular detection of acrA gene

PCR assay using specific primers for *acr*A gene demonstrated that all ciprofloxacin-resistant strains harbored *acr*A gene and consequently contain AcrAB efflux system. PCR amplification products of *acr*A gene among clinical ciprofloxacin-resistant isolates was shown in Figure 1, the expected 495 bp DNA fragment was belonged to *acr*A gene. Sequence analysis showed that these amplification products corresponded to *acr*A gene of *Klebsiella pneumoniae*.

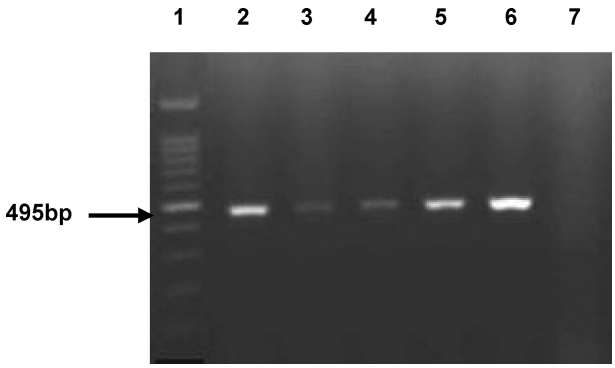

Figure 1: PCR amplification of *acrA* gene in ciprofloxacin-resistant *Klebsiella pneumonia*
Lane 1: 1500 bp DNA size marker; Lane2: Positive control for *acrA* gene; 3–6: PCR product of *acr*A gene (495 bp) in ciprofloxacin-resistant *K. pneumonia* strains; Lane 7: negative control.

Table 1: MICs of ciprofloxacin with and without CCCP in *K. pneumonia* isolates

Fold reduction in MICs	Number of strains	MICs of Ciprofloxacin (µg ml^{-1})	MICs of Ciprofloxacin after adding 25 µg ml^{-1} CCCP
32	2	128	4
16	1	128	8
8	1	256	32
8	1	128	16
8	4	32	4
4	3	256	64
4	1	16	4
2	3	256	128
2	1	32	16
2	1	64	32
2	1	8	4
0	12	256	256
0	6	32	32
0	1	64	64
0	2	16	16

3.3 Inhibitory effect of CCCP on the AcrAB efflux system

MIC value for ciprofloxacin resistance was determined in presence of 25 µg ml^{-1} of CCCP as efflux pump inhibitor to evaluate the role of active AcrAB efflux system in resistance to ciprofloxacin among CIP-resistant isolates. Comparison of MIC value with and without CCCP showed a significant reduction from 2- to 32-fold after using 25 µg ml^{-1} of CCCP among 19 out of 40 (47.5%) ciprofloxacin-resistant isolates. Among these former isolates 2 (10.6%) isolates showed 32-fold reduction in MIC, 1 (5.2%) isolate showed 16-fold reduction, 6 (31.6%) isolates8-fold, 4 (21%) isolates and 6 (31.6%) isolates showed 4-fold and 2-fold reduction in MIC, respectively. Twenty-one out of 40 (52.5%) ciprofloxacin-resistant isolates illustrated no differences in MIC value before and after using CCCP (Table 1).

4 Discussion

Recent studies indicated that emergence of ciprofloxacin-resistant clinical isolates and multidrug resistant *K. pneumoniae* strains have been increased among burn patients in Iran [24], [25]. Burn patients are at the high risk of gram negative bacilli including *K. pneumoniae* infections, especially in the pediatric burn cases when infected with multidrug resistant strains [26], [27]. Present study demonstrated that 95% of ciprofloxacin-resistant isolates were multidrug resistant indicating the importance of MDR strains of *K. pneumoniae* among burn patients. Recent studies indicated many different mechanisms for antimicrobial resistance ability among bacteria; one of the most important mechanisms is efflux pumps including AcrAB efflux system. Many studies have been performed to investigate the relation between AcrAB efflux system and resistance to fluoroquinolones in *K. pneumoniae* [3], [28] and other bacteria [6]. Different inhibitors including phenylalanine arginine β-naphthylamide (PAβN) or carbonyl cyanide 3-chlorophenylhydrazone (CCCP) have been used to evaluate the effect of AcrAB efflux pump in ciprofloxacin resistance property among *K. pneumoniae* strains [28], [29].

In the present study, MICs of ciprofloxacin were measured with and without CCCP as an AcrAB efflux pump inhibitor. The results revealed that 47.5% of ciprofloxacin-resistant isolates showed reduction from 2- to 32-fold in MICs of ciprofloxacin after using CCCP which is represented the high resistance to ciprofloxacin (over 256 µg ml^{-1}) among isolates. The results of this study in reduction of MICs after using CCCP are consistent with other studies [29]. In another study performed by Hasdemir and colleagues (2004), it has been revealed that AcrAB efflux pump contribute to resistance to quinolones, chloramphenicol, tetracycline, and β-lactams in multidrug resistant *K. pneumonia* isolated from Turkey [28]. In the present study, simultaneous resistance to ciprofloxacin, tetracycline and β-lactams was observed among isolate with reduction in MICs to ciprofloxacin after using CCCP. Although, the PCR assay showed that all the ciprofloxacin-resistant isolates harbored the *acr*A gene but 47.5% of isolated showed reduction in MICs to ciprofloxacin after using CCCP, which is confirmed the contribution of AcrAB efflux pump in ciprofloxacin resistance in these isolates. In the study by Hasdemir and colleagues (2004), reduction in MICs to ciprofloxacin after using pump inhibitor has been reported among 39% of isolates. In the present study, the remaining 52.5% of isolates showed no changing in MICs after using CCCP thus other mechanisms as mutation in target proteins of DNA gyrase and topoisomerase IV enzymes or harboring the *qnr* genes which are responsible for resistance to fluoroquinolones probably involved in ciprofloxacin resistance of the strains [22], [30].

5 Conclusions

In conclusion the AcrAB efflux system is one of the major mechanisms in multidrug resistant *K. pneumoniae* strains. Ciprofloxacin acts as substrate for AcrAB efflux pump and consequently reduces the intracellular concentration of antibiotics. In this study, the relation between AcrAB efflux pump and resistance to ciprofloxacin was confirmed.

Notes

Competing interests

The authors declare that they have no competing interests.

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