The Impact of Fluoroquinolones use on Antibiotic Resistance in an Intensive Care Burn Department

Lamia Thabet*, Monia Memmi***, Amel Turki*, Amen Allah Messadi**.

*- Laboratory of biology. **-Burn unit, ***-Service of Pharmacy, Aziza Othmana Hospital

L. Thabet, M. Memmi, A. Turki, A. A. Messadi.

L'impact des fluoroquinolones sur la résistance aux antibiotiques dans une unité de soins des brulés

LA TUNISIE MEDICALE - 2010 ; Vol 88 (n°05) : 296 - 300

L. Thabet, M. Memmi, A. Turki, A. A. Messadi.

The impact of fluoroquinolones use on antibiotic resistance in an intensive care burn department

LA TUNISIE MEDICALE - 2010 ; Vol 88 (n°05) : 296 - 300

RÉSUMÉ

Prérequis : L'utilisation des fluoroquinolones (FQ) a été identifié comme un facteur de risque de colonisation et d'infection à Staphylococcus aureus résistant à la méthicilline (SARM), Pseudomonas aeruginosa multirésistant(PMR), Acinetobacter multirésistant(AMR) et bactérie multirésistante(BMR).

But : Notre étude se propose de mesurer la consommation annuelle des FQ et la résistance aux antibiotiques chez Staphylococcus aureus, P. aeruginosa, K. pneumoniae et A .baumannii dans un service de réanimation des brûlés.

Méthodes : L'étude a été conduite durant une période de quatre ans (1 Janvier 200 au 31 Décembre 2003). L'étude de la sensibilité aux antibiotiques a été réalisée par la méthode de diffusion selon les recommandations de la Société Française de Microbiologie. La consommation des antibiotiques suivants : ofloxacine et ciprofloxacine a été calculée selon la densité antibiotique qui tient compte de la quantité consommée en grammes et des doses définies journalières, rapportés ensuite pour 1000 journées d'hospitalisations. Une corrélation est considérée comme statistiquement significative si p<0, 05.

Résultats : La consommation de la ciprofloxacine est significativement associée à l'émergence de souches de P. aeruginosa résistant à cette molécule (cc=0, 95, p<0, 05). Par ailleurs, la consommation de la ciprofloxacine est significativement corrélée à l'émergence de la résistance à l'imipénème (cc=0, 95, p<0. 05) et à la ceftazidime(cc=0, 95, p<0, 05) chez P. aeruginosa. La restriction de l'utilisation de la ciprofloxacine a été faite durant l'année 2003, elle a été suivie par une baisse significative de la résistance à l'imipénème, ceftazidime et ciprofloxacine chez P. aeruginosa. L'utilisation des FQ est significativement corrélée avec l'émergence de SARM(cc=0, 96, p<0, 05). La restriction de l'utilisation des FQ est significativement corrélée avec la baisse de SARM (p<0, 05). La consommation de la ciprofloxacine est également corrélé avec la résistance à la ceftazidime chez K. pneumoniae. Cependant, on n'a pas trouvé de corrélation significative entre la consommation de la ciprofloxacine et la résistance chez A. baumannii aussi bien pour la ciprofloxacine que pour l'imipénème et la ceftazidime.

Conclusion : Notre étude illustre bien la pression de sélection de l'utilisation des fluoroquinolones sur le développement des BMR. L'utilisation et la durée de traitement avec ces molécules devraient êtres limitées afin de contrôler l'émergence de BMR.

Mots-clés

Fluoroquinolones, consommation, SARM, BMR, Pseudomonas aeruginosa, Klebsiella pneumoniae, Acinetobacter baumannii

SUMMARY

Background: Fluoroquinolones (FQ) use has been identified as a risk factor for colonization and infection to methicillin resistant Staphylococcus aureus(MRSA), Pseudomonas aeruginosae multiresistant(PMR) , Acinetobacter multiresistant (AMR) and multidrug resistant bacteria(MDRB).

Aim : Our study proposes to measure the annual antibiotic use of FQ and antimicrobial resistance in P. aeruginosa, S. aureus, Klebsiella pneumoniae and A. baumannii in an intensive care burn unit.

Methods : The study was conducted during a 4 year period (1 January 2000 to 31 December 2003). Antimicrobial susceptibility testing was performed using the disk diffusion method as recommended by the French Society of Microbiology. The consumption of the following antibiotics: ofloxacin, ciprofloxacin was expressed as the antimicrobial use density (AD) taking into account the quantity of antibiotics in Grams converted to defined daily doses (DDD) and the number of day hospitalization. Statistical significance was defined as p value < 0. 0 5 for the corresponding correlation coefficient.

Results : There were statistically significant relationship between use of ciprofloxacin and resistance in P. aeruginosa to this drug (rs=0. 95, p<0. 05). Moreover, the ciprofloxacin consumption was correlated with resistance to imipenem (rs=0. 95, p<0. 05) and ceftazidime (rs=0. 95, p<0. 05) in P. aeruginosa . A restriction use of ciprofloxacin has been taken during 2003, it is folowed by a significant decrease of resistance to imipenem, ceftazidime and ciprofloxacin in P. aeruginosa (p<0, 05). The use of fluoroquinolones was correlated significantly with MRSA (rs=0. 96, P<0. 05) . The restriction use of FQ was significantly associated with a decrease of MRSA. The consumption of ciprofloxacin was also correlated (P<0. 05) with resistance of ceftazidime in K. pneumoniae. However, there is not a correlation (P> 0. 05) between fluoroquinolones use and resistance in A. baumannii as well in ciprofloxacin, imipenem and ceftazidime. Our study illustrates the pressure of selection of fluoroquinolones use in the development of MDRB. The use and or the duration of treatment with theses antibiotics should be rationalised as part of efforts to control the emergence of multidrug resistant bacteria

Key-words

fluoroquinolones use, multidrug resistance bacteria, MRSA, Pseudomonas aeruginosa, Acinetobacter baumannii, Klebsiella pneumoniae.

تأثير " الفليوروكينولون " على مقاومة الضادات الحيوية في قسم معالجة المصابين بالحروق.

الباحثون : لمياء ثابت - منية مامي - أمال التركي - أمان الله المسعدي.

الكلمات الأساسية : "الفليوروكينولون - " استهلاك " - البسيدوموناس آريجينوزا " - "كلابسيلابنومونيا "

During the two last decades, fluoroquinolones (FQ) use has significantly increased in the word (Europe, USA). This increase was associated with higher rates of bacterial resistance to these antibiotic (1, 2, 3). In addition, fluoroquinolones use has been identified as a risk factor for colonization and infection to methicillin resistant Staphylococcus aureus (MRSA), Pseudomonas aeruginosa multiresistant (PMR) , Acinetobacter multiresistant (AMR) and multidrug resistant bacteria (MDRB) (4, 5).

Our study proposes to measure the annual antibiotic use of FQ and antimicrobial resistance in P. aeruginosa, S. aureus, Klebsiella pneumoniae and A. baumannii in an intensive care burn unit.

MATERIALS AND METHODS

Patients and methods

1-Data Collection :

a-Description of the intensive care burn department and patients

The intensive care burn unit comprises 16 beds and is the only one specialized in the management of burned patients in the country. Consequently patients hospitalized in this unit come from the emergency of the hospital as well as from transfers from other hospitals.

The study was conducted during a 4 year period (1 January 2000 to 31 December 2003), 836 patients were hospitalized during this period. The average number of admissions was 204 per year and the mean number of patient days 4036 per year. In the unit, antimicrobials were empirically prescribed before the results of antimicrobial susceptibility testing.

The causes of burns were dominated by home accident (59. 7%), followed by industrial accident (23. 7) and the suicide attempts (16. 6%). The nature of burn was thermal (70%), electric (27%) and chemical (3%). The average of burned cutaneous surface was 44%.

Total mortality was 18% whereas septic mortality was 34. 6%.

b- Antimicrobial susceptibility

Antimicrobial susceptibility testing was performed using the disk diffusion method as recommended by the French Society of Microbiology (5). All susceptibility data were stored in a laboratory data base using WHONET software 5. 3 (6). Duplicate isolates defined as repeated isolation of the same bacterial species for the same patient with the same profile of antibiotic susceptibility were excluded. The number of resistant bacteria isolates was reported per 1000 days of hospitalization (DH).

C-antibiotic consumption:

The data on antibiotic consumption were collected from the pharmacy computer system. The consumption of the following antibiotics: ofloxacin, ciprofloxacin was expressed as the antimicrobial use density (AD) taking into account the quantity of antibiotics in Grams converted to defined daily doses (DDD) and the number of day hospitalization (7). The defined daily doses (DDD) were those proposed by WHO (7) and correspond to the antibiotic amount used in the most frequent indication for a route of administration. The calculation of AD for each molecule was carried out according to the following formula:

AD= Quantity consumed in Grams for the particular antimicrobial X 1000 DDD for that antimicrobial X number of Day hospitalizations

This expressed as DDD per 1000 DH.

A restriction of use of Fluoroquinolones (ofloxacin and ciprofloxacin) was established at the burn unit during 2003.

2 Data analysis: Statistical analysis was conducted to explore the relationship between antibiotic use and resistance of bacteria. SPSS software was used to calculate the Spearman rank correlation coefficient (r s). Statistical significance was defined as p value < 0. 0 5 for the corresponding correlation coefficient.

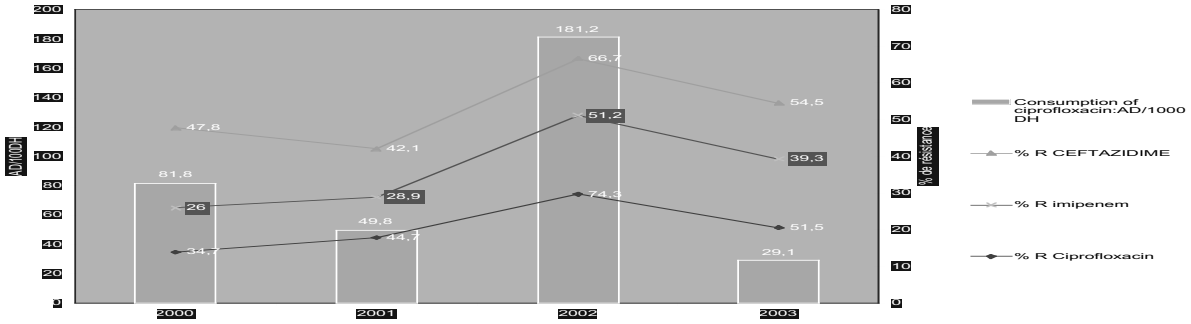
RESULTS

1-Antimicrobial resistance

There were statistically significant relationship between use of ciprofloxacin and resistance in P. aeruginosa to this drug (rs=0. 95, p<0. 05). Morover, the ciprofloxacin consumption was correlated (rs=O. 95, p<0. O5) with resistance to imipenem (rs=0. 95, P<0. 05) and ceftazidime in P. aeruginosa (Fig 1). A restriction use of ciprofloxacin has been taken during 2003, it is folowed by a significant decrease of resistance to imipenem, ceftazidime and ciprofloxacin in P. aeruginosa (P<0, 05).

The use of ciprofloxacin was correlated significantly with MRSA (rs=O. 96, P<0. 05) . The restriction use of FQ was significantly associated with a decrease of MRSA (Fig 2).

Figure 1 : correlation between ciprofloxacin consumption and ciprofloxacin, imipenem , ceftazidime resistance in P.aeruginosa



The consumption of ciprofloxacin was also correlated (P<0, 05) with resistance of ceftazidime in K. pneumoniae (Fig3).
However, there is not a correlation (P> 0. 05) between fluoroquinolones use and resistance in A. baumannii as well in ciprofloxacin, imipenem and ceftazidime (Fig 4).

Figure 2 : Correlation between fluoroquinolones consumption and MRSA

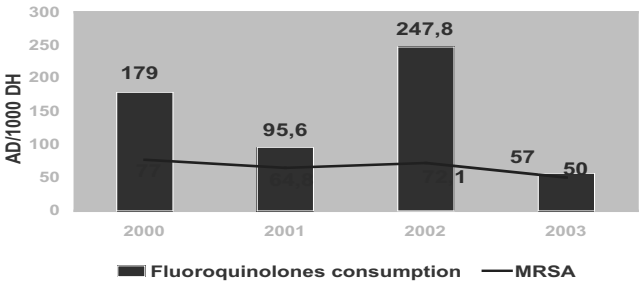


Figure 3 : Correlation between ciprofloxacin consumption and resistance to ceftazidime in K.pneumoniae

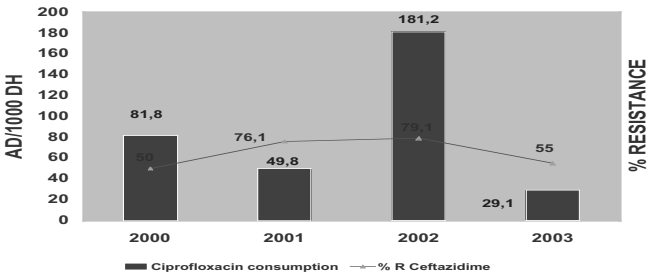
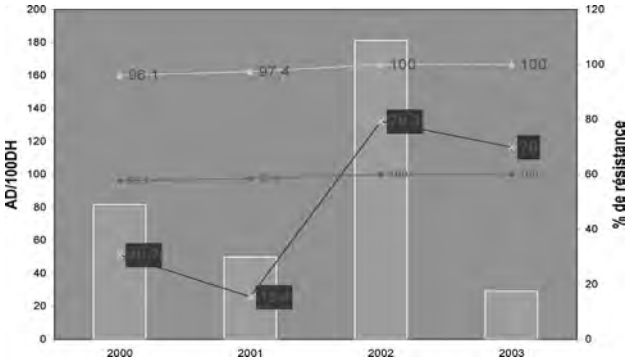


Figure 4 : association between ciprofloxacin consumption and ciprofloxacin, imipenem , ceftazidime resistance in A.baumannii



DISCUSSION

The prevalence of multidrug antimicrobial resistant bacteria is increasing among ICU patients causing a major concern worldwide. Antibiotic use is among factors incriminated in this increase of resistance. However the relationship between antibiotic consumption and resistance to these drugs is complex and it is no easy to find a correlation in all cases (9, 10).
In our study, ciprofloxacin use was significantly correlated with resistance in P. aeruginosa to this drug (p<0, 05). In addition the ciprofloxacin use was correlated with imipenem and ceftazidime resistance in P. aeruginosa (P<0, 05). Elisabeth paramythiotou (11) report that the ciprofloxacin therapy was associated with multidrug resistant Pseudomonas aeruginosa acquisition (MDRPA). Similary, Nseir (2) reported that fluoroquinolones use has been identified as risk factor for colonization and infection to MDRPA acquisition. Patterson et al reported « collateral damage » from fluoroquinolones therapy; the authors found a correlation between quinolones use and quinolones resistant Gram negative bacilli including P. aeruginosa (12).
Fluoproquinolones use was also significantly correlated with MRSA in our study (p<0. 05). This observation is consistent with the results of others studies linking FQ use to MRSA (2, 4). Charbonneau et al (13) report that the exposure to FQ was an independent factor for MRSA acquisition. The authors report that the restriction use of FQ, during one year was followed by a decrease of MRSA. In our study the restriction use of FQ in 2003 was also followed by a decrease of MRSA (p<0. 05).
Fluoroquinolones use was associated with resistance in both pathogens S. aureus and P. aeruginosa as well in our study as in anothers studies (2, 4, 13). Athough the pathways of selection of resistance differ between the two pathogens. Fluoroquinolnes resistant in P. aeruginosa is believed to arise largely from the selection of organisms with point mutations in the topoisomerase enzymes that are targets for the FQ (4). This hypothesis is supported by studies demonstrating the emergence of resistance during therapy with FQ.
For methicillin resistant S. aureus, de novo emergence of resistance as seen with P. aeruginosa is not a common event, rather patients are generally believed to acquire methicillin resistant strains of S. aureus from the environnement (eg through cross transmission), antimicrobial drug use many increase the likehood of colonization or amplify the resistant population after colonization. Fluoroquinolones are not active against most methicillinoresistant isolates providing a selective pressure for MRSA. While any antimicrobial agent that is not active against MRSA should increase a patient's risk for infection, FQ my be particularly likely to do so, since they have appear to have unique effects on the expression of MRSA resistance determinants and fibrinonectin binding proteins (4).
Concerning A. baumannii, there is not a correlation between fluoroquinolones consumption and resistance in our study. However Nseir and collegueas reported that fluoroquinolones use has been identified as a risk factor for colonization and infection to multidrug resistant A. baumannii (2). The cause of emergence and spread of antimicrobial resistance pathogens seem to be multifactorial. Acquisition of organisms from the hospital environment is also one among factors incriminated in emergence of resistance, particularly in A. baumannii.
Concerning K. pneumoniae, ciprofloxacin use was significantly correlated with ceftazidime resistance (p<0, 05) as Nseir and colleagues have observed (1). Hsueh et al similarly reported

that fluoroquinolones use was correlated with increased incidence of ceftazidime resistance in K. pneumoniae (3).

CONCLUSION

Our study illustrates the pressure of selection of fluoroquinolones use in the development of resistance in P. aeruginosa. It supports in the same way the "collateral damage" of use of theses molecules on the resistance to betalactams particularly to imipenem, ceftazidime and methicillin. The use and or the duration of treatment with theses antibiotics should be rationalised as part of efforts to control the emergence of multidrug resistant bacteria

Références

1. Nseir S, Dipompeo C, Soubrier S, Delou P, Leuci H, Fabienne M, Durocher A. First generation fluoroquinolone use and subsequent emergence of multiple drugs resistant in the intensive care unit. Critical Care Medicine2005; 33:283-9.
2. Seir N, Ade Fr, Marquette CH, Durocher A. Impact de l'utilisation des fluoroquinolones sur l'émergence des bactéries multirésistants. Path.Bio2005; 53:470-5.
3. Hsueh P, Chen, Luh K. Relationship between antimicrobial use and antimicrobial resistance in Gram negative bacteria causing nosocomial infections from 1991-2003 at a university hospital in Taiwan. Int J Antimicrob Agents 2005;26:463-72.
4. Macdougall C, Harpe S, Powell J, Jhonson C, Edmont M, Polk R. Pseudomonas aeruginosa,Staphylococcus aureus and fluoroquinolone use. Emerging Infectious Diseases 2005; 11:1-14.
5. Mohr J, Jones A, Zeichner L, Wanger A, Tilloston G. Associations between antibiotic use and changes in susceptibility patterns of Pseudomonas aeruginosa in a private university affiliated teaching hospital: an 8 year experience: 1995-2002. Int J Antimicrob Agents 2004 ; 11:346-51.
6. C J Soussy. Comité de l'antibiogramme de la SFM. Bull. Soc. Fr. Microbiol. 2001.
7. www.who.int/drugresistance/whonet software.
8. Mise en place d'un réseau de surveillance de la consommation des antibiotiques parallèlement à certaines résistances bactériennes dans les établissements de soins de l'inter région Paris Nord. Protocole ATB 2005, CCLIN Paris Nord. http : www.ccr.jussien.fr/cclin.
9. Carmeli Y, Troillet, G N .Eliopoulos,.Samore M. Emergence of antibiotic resistant Pseudomonas aeruginosa: comparison of risks associated with different antipseudomonal agents. AAC 1999; 43:1379-82.
10. Lozzano J, Monnet D, Yague A,Campillos P, Gonzalo N, Burgos A. Surveillance de la résistance bactérienne et modélisation de sa relation avec les consommations d'antibiotiques au moyen de l'analyse des séries chronologiques. Bull.Soc.Fr. Microbiol 2002 ; 17 :
11. Elisabeth .Paramythiotou, J. Lucet, J. Timsit, D. Vanjak, C .Butz, A.Andremont. Acquisition of multidrug resistant P.aeruginosa in patients in intensive care units: role of antibiotic with antipeudomonal activity. CID 2004 ; 38: 670-4.
12. Patterson D « collateral damage from cephalosporin or quinolone antibiotic therapy.CID 2004; 38:41-5.
13. Charbonneau P, Parienti PP, Thibon P, Lebouvier G , Leclerq R.Facteurs d'acquisition du SARM à l'Hôpital :rôle des fluoroquinolones. 2005;35 :35-7
14. Neuhauser MM, Weinstein R, Rydman R, Danziger L, Quinn K. Antibiotic resistance among Gram negative bacilli in US intensive care units: implications for fluoroquinolone use. JAMA 2003; 289:885-8.
15. Polk R, Jhonson C,Edmonnd M, wenze Rl. Trends in fluoroquinolone(FQ) prescribing in 35 us hospitals and resistance for P.aeruginosa a scope MMIT report. In proceeding of the interscience conference on antimicrobial agents and chemotherapy, Chicago American Society for Microbiology 2001(Abstract UL-1).